Towards the Development, Application and Understanding of Copper-Catalysed Alkene Functionalisation Processes Using Iodonium Salts

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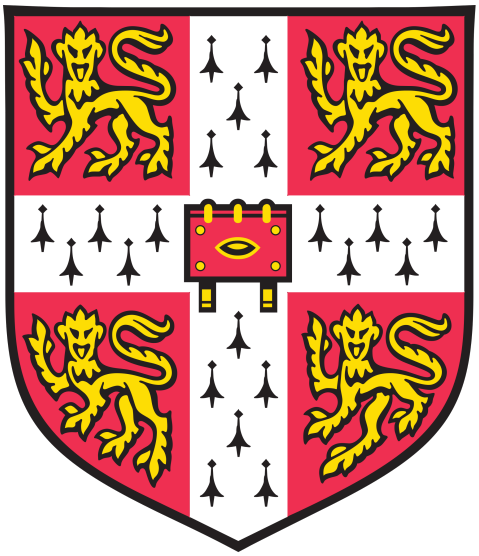

This dissertation is submitted for the Degree of Doctor of Philosophy

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i Declaration

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes the work carried out in the Department of Chemistry from October 2013 to June 2017. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

Henry Peter John Male

13 September 2017

ii Statement of Length

This dissertation does not exceed the word limit of 60,000 as set by the Degree Committee for the faculty of Physics and Chemistry.

Henry Peter John Male

13 September 2017

iii Acknowledgements

First, I would like to thank Matt for giving me the opportunity to work in his lab. It's been a great experience. I've learnt a huge amount from my time in the Gaunt group and I'm very grateful to have been allowed to work on the projects that I have. Thank you.

Secondly, I need to thank the people who have been unlucky enough to work with me: Elise, Matthieu, Dean and Dominik. I couldn't have been more fortunate with the colleagues that I've researched alongside. Thanks for all the help, all the conversations, and all the work you've shared with me. My PhD wouldn't have been the same without you all.

I'd like to extend my thanks to the wider membership of the Gaunt lab (both past and current), particularly as many of them have dedicated their time to proofreading this thesis. More generally, though, I'm grateful for the incredible environment of the group. It's been a real honour to work with people who are so enthusiastic and knowledgeable about the science that they do. Even more importantly, I'm grateful for their friendship. I'm particularly indebted to Ben and Jamie who have also had the dubious honour of living with me for two years. Their support (or rather, their willingness to go to the pub) has been vital for getting me through the last four years. Thank you.

I'm also grateful to my friends outside the lab. There is very little chance that I'd have stayed as sane as I have (I know) without you all. It's been fantastic to be able to escape chemistry to talk to some people who have different interests and lives, but who are always, or at least usually, willing to listen to me.

To Jo - thank you for the last two years. I'm so grateful for your interest in what I do and for your tolerance of me when I'm being miserable. You've got me through a huge amount. You're the best.

Next, I need to thank my family. I don't know where I'd be if it wasn't for the bedrock and inspiration that they provide. They might have absolutely no clue about my chemistry, but I wouldn't have been able to do any of it without them. I'm eternally grateful for their sense of humour, card-playing abilities and aptitude in the kitchen. I couldn't be luckier to have the family that I have.

Finally, to Mum and Dad - there is no way that I'd be in the position that I'm in without your support, generosity and love. I can't thank you enough for all you've done for me. This thesis is for you.

iv Abstract

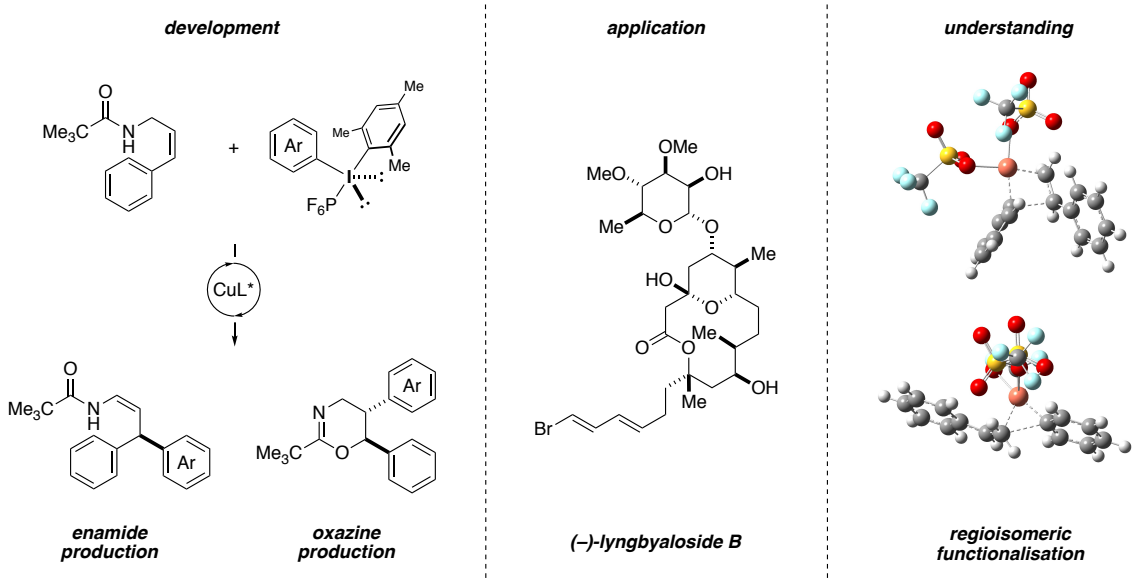
Towards the Development, Application and Understanding of Copper-Catalysed Alkene Functionalisation Processes using Iodonium Salts

This thesis comprises three projects focused on the use of the combination of catalytic copper and iodonium salts towards the functionalisation of alkenes.

Chapter 2 details the development of an enantioselective and regiodivergent allylic amide arylation procedure using a specific copper(II)-bisoxazoline pre-catalyst and hexafluorophosphate diaryliodonium salts. The regioselectivity of the process was discovered to be controlled by the electronic properties of the iodane employed, allowing enamide production to be biased with electron-poor iodonium salts and oxazines to be produced with electron-rich analogues. An overall scope of 38 compounds was collaboratively elaborated, with 20 synthesised personally. All products were generated in useful yields and high levels of enantioselectivity.

Chapter 3 describes efforts towards the application of a copper-catalysed *oxy*-alkenylation procedure to the production of the macrolidal natural product (–)-lyngbyaloside B. It is proposed that an elaborate homoallylic carbamate may be coupled with a complex polyoxygenated alkenyl(aryl)iodonium salt as a fragment coupling for polyketide synthesis. Following extensive investigations, it was discovered that the challenging vinyl-iodonium salt could be synthesised in good yields and then coupled with the desired homoallylic carbamate, albeit in limited yield and low *d.r.*.

Chapter 4 presents initial studies towards a computational understanding of the copper-catalysed arylation of alkenes with iodonium salts. Evidence is presented to suggest that two functionalisation modes are energetically accessible, allowing the production of regioisomeric arylated products.



v Abbreviations

Å	Angstrom
Ac	acetyl
aq.	aqueous
Ar	undefined aryl group
ASAP	atmospheric pressure solids analysis probe
ATR	attenuated total reflectance
BOX	bisoxazoline
BP86	Becke 1988 exchange/Perdew 1986 correlation functionals
Bn	benzyl
n-Bu	normal butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C	Celsius
cat.	catalytic
cm^{-1}	wavenumbers
CMD	concerted metalation-deprotonation
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
δ	chemical shift
Δ	reflux/difference

dba	dibenzylideneacetone
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIPEA	*N*,*N*-di*iso*propylethylamine
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DPE	diphenylethylene
d.r.	diastereomeric ratio
DTBP	2,6-di-*tert*-butylpyridine
ECP	effective core potential
e.e.	enantiomeric excess
EI	electron impact
Elec	electrophile
equiv.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
FID	flame ionisation detector
g	gram(s)
G	Gibb's energy

GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
h	hours
HMDS	hexamethyldisilazane
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IAT	iodine atom transfer
IEFPCM	integral equation formalism polarization continuum model
IR	infrared
IRC	intrinsic reaction coordinate
$\tilde{J}$	coupling constant
L	undefined ligand
LCMS	liquid chromatography-mass spectrometry
m	multiplet
m	mass
M	molar
Me	methyl
Mes	mesityl
MHz	megaHertz
mg	milligram(s)

µg	microgram(s)
mL	millilitre(s)
µL	microliter(s)
mmol	millimole(s)
µmol	micromole(s)
mol	mole(s)
MS	molecular sieves
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
OTf	trifluoromethanesulfonate (triflate)
P	undefined protecting group
PIFA	bis(trifluoroacetoxy)iodobenzene
ppm	parts per million
Ph	phenyl
i-Pr	*iso*propyl
Py	pyridine
QZVP	quadruple-ξ valence polarisation
R	variable group (Markush)
R_F	retention factor
rt	room temperature

q	quartet
qn	quintet
s	singlet
sat.	saturated
SCRF	self-consistent reaction field
SDD	Stuttgart/Dresden pseudopotential
SET	single electron transfer
SM	starting material
SVP	single-ξ valence polarisation
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
TC	thiophene-2-carboxylate
TES	triethylsilyl
THF	tetrahydrofuran
THP	Tetrahydro-2*H*-pyran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
X	Unspecified group (typically heteroatomic or halogen)
Y	Unspecified group (typically metallic or semimetallic)
z	charge

vi Table of Contents

1 Introduction – The Catalytic Generation and Reaction of Aryl and Alkenyl Cation Equivalents

This introduction describes the development of catalytically-generated aromatic and vinyl electrophiles and their application in C–C bond-forming reactions. The success that has been achieved with the use of palladium(II) species as transient electrophilic equivalents is discussed before the argument is extended to copper(III). It is demonstrated that the combination of copper salts and iodonium salts provides a powerful platform for the functionalisation of nucleophiles, especially carbon-based functionalities.

1.1 sp^2-Hybridised Carbon Electrophiles

Arenes and alkenes are two of the most fundamental functional groups in organic chemistry. The exploitation of these planar moieties has allowed for the development of classes of molecules crucial to modern life. Such compounds include materials, pharmaceuticals and agrochemicals (Figure 1).

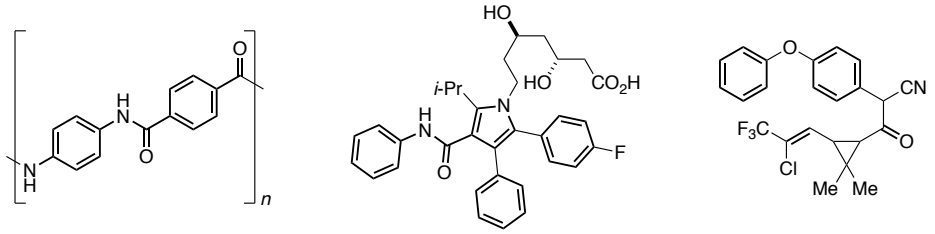
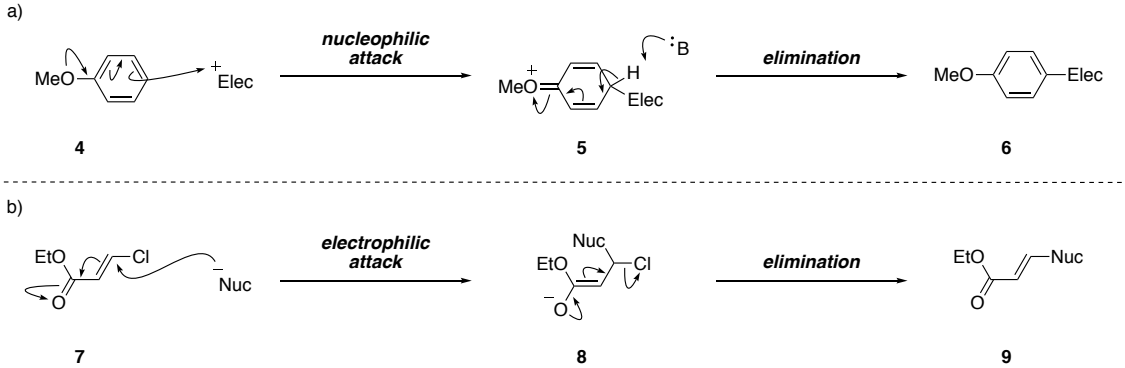


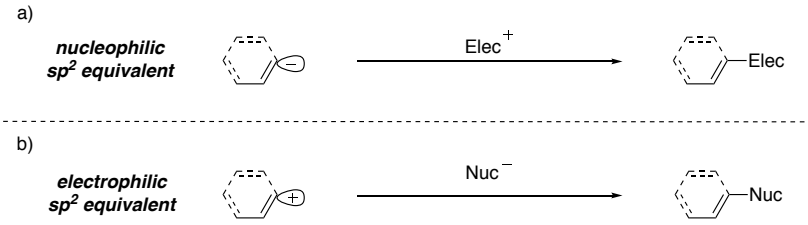
Figure 1 – Examples of commercially and societally important compounds bearing sp^2-hybridised groups: Kevlar™ **1**, a synthetic fibre; Lipitor™ **2**, a statin; and λ-cyhalothrin **3**, a pesticide

One method for the generation of complex aromatic and vinylic species is to functionalise a simple arene or alkene core. Many such processes exploit the electronic properties of the π-systems of aromatic groups and olefins. An example of π-nucleophilicity can be seen in the Friedel-Crafts reaction (Scheme 1a) whilst π-electrophilicity is exemplified by addition-elimination (Scheme 1b).



Scheme 1 – a) Friedel-Crafts π-nucleophilicity and b) addition-elimination π-electrophilicity

An alternative strategy to generate the same classes of product as above is through the reaction of some sp^2-hybridised nucleophile or electrophile equivalent (Scheme 2).



Scheme 2 – Conceptual description of a sp^2-hybridised group a) nucleophile and b) electrophile

A wide variety of nucleophilic sp^2-equivalents are routinely used in organic synthesis. Such reactive species include, amongst many others, Grignards reagents and organolithiums (Figure 2a). Contrastingly, stoichiometric sp^2-hybridised electrophiles are less widely used and are more limited in scope, largely being constrained to high-valent aryl- and alkenyl-main group compounds (Figure 2b).

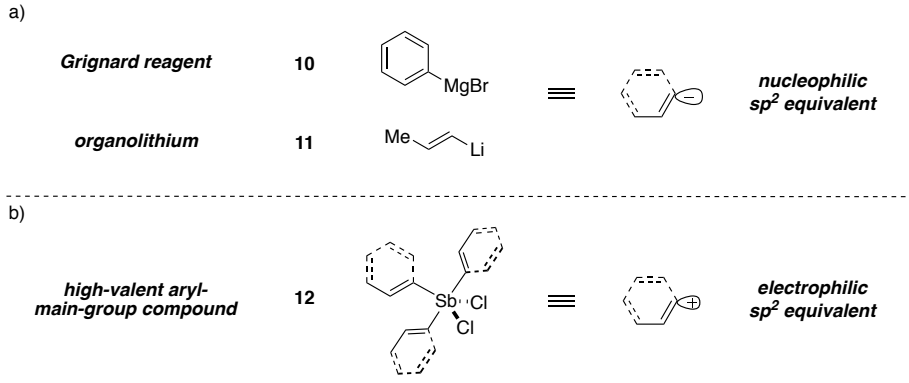
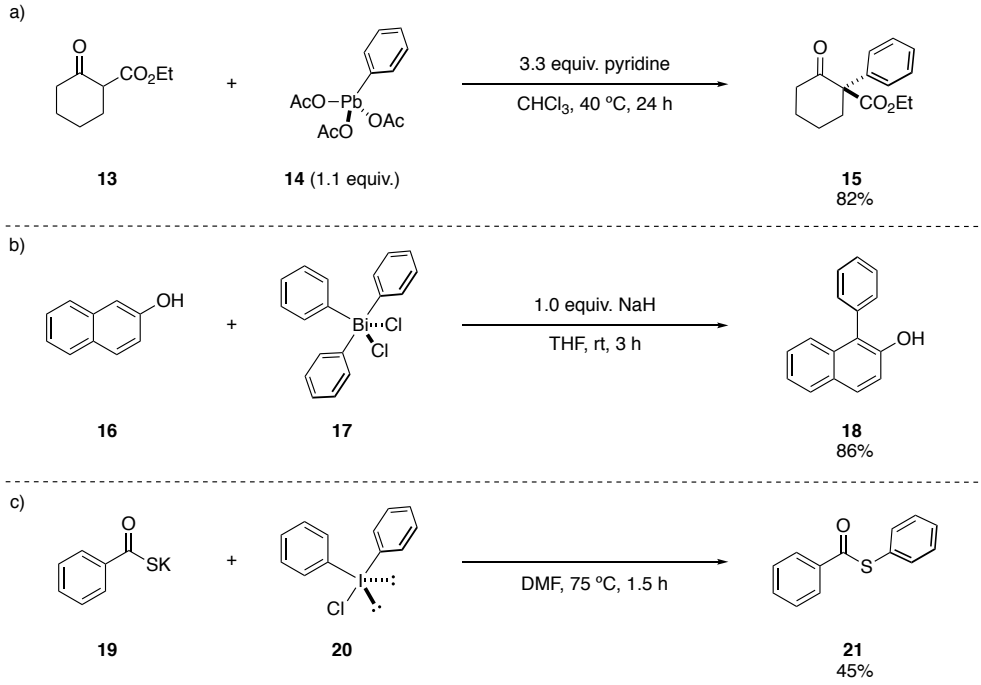


Figure 2 – Representative synthetic equivalents for a) an sp^2-hybridised nuceleophile and b) an sp^2-hybridised electrophile

Lead(IV),[1] bismuth(V)[2] and iodine(III)[3] species have all been employed towards the arylation and vinylation of numerous nucleophile classes. For example, phenyllead triacetate has been observed to arylate malonates, triphenylbismuth dichloride has been used to generate arylated napthols and diaryliodonium salts have been used to functionalise thiocarboxylates (Scheme 3).[4–6]



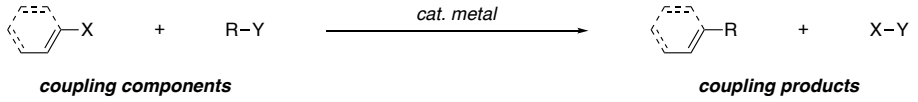
Scheme 3 – a) Kozyrod's malonate arylation with lead(IV) reagent **14**;[4] b) Barton's 2-napthol arylation with bismuth(V) reagent **17**;[5] c) You and Chen's thiocarboxylate arylation with iodine (III) reagent **20**[6]

Despite the operational simplicity of arylation reactions using high-valent main-group compounds, the use of these reagents is far from ideal. Lead is toxic, bismuth has a low abundance and the reaction of iodanes requires relatively forcing conditions with even strong nucleophiles. Attention has therefore been directed towards the development of catalytically-generated and highly reactive sp^2-hybridised electrophile equivalents. This introduction discusses progress towards such intermediates, first addressed by an overview of palladium catalysis before the concept is extended to powerful copper-catalysed methods employing hypervalent iodine reagents such as **20** to functionalise even poor nucleophiles.

1.2 Palladium-Catalysed Generation and Reactivity of sp^2 Electrophile Equivalents

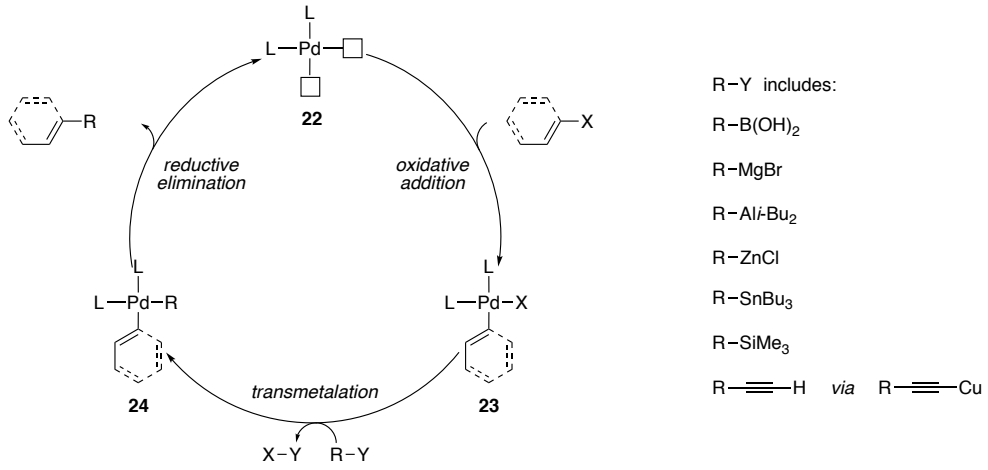
1.2.1. Palladium-catalysed cross-coupling

The development of cross-coupling has had an undeniably huge impact on modern chemistry. The importance of this work for allowing the development of new disconnections for chemical synthesis is highlighted by the awarding of the 2010 Nobel Prize to Richard Heck, Akira Suzuki and Ei-ichi Negishi for their contributions to the field. Despite the very broad uses of the reaction, the underlying principle of cross-coupling is very simple: a metal catalyst is employed to connect an aryl, alkenyl or even alkyl (pseudo)halide with a nucleophile (Scheme 4). Although a variety of elements have been observed to be competent coupling catalysts (including the first-row transition metals iron,[7] copper,[8] and nickel[9,10]), palladium is by far the most widely-used.[11]



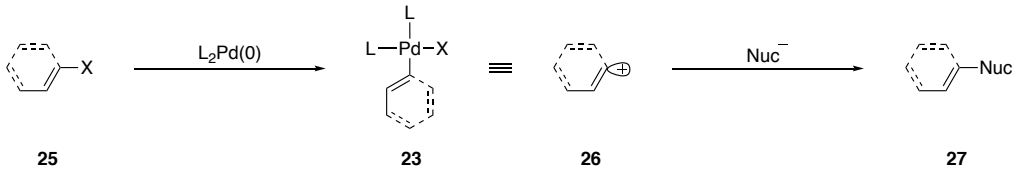
Scheme 4 – Simplified cross-coupling procedure

The broad use of palladium can be attributed to the well-defined organometallic behaviour of the metal centre, allowing the key mechanistic steps of cross-coupling to be characterised, understood, and manipulated (Scheme 5).[12] At the simplest level, the active catalyst in palladium-catalysed cross-coupling is the 14-electron palladium (0) species **22**, generated *in situ* by ligand dissociation or by a reduction process from an introduced palladium(II) source. Oxidative addition of complex **22** into an aryl/vinyl (pseudo)halide furnishes stable 16-electron palladium (II) adduct **23**. **23** then undergoes transmetalation with a nucleophilic equivalent to give nucleophile-bound complex **24** before reductive elimination occurs to give the coupled product and to regenerate the Pd(0) catalyst.



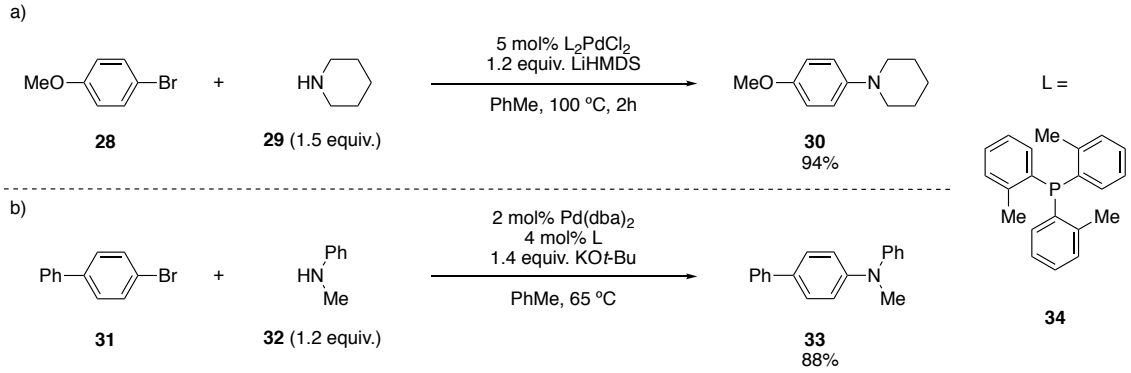
Scheme 5 – Simplified cross-coupling mechanism

The consistency of the behaviour of palladium has allowed for the coupling of a broad range nucleophilic species to aryl and vinyl (pseudo)halides.[11] Boronic acids,[13] Grignard reagents,[14] organozincs,[15] organotin species[16] and copper acetylides[17] are all commonly-employed coupling partners. As such, Palladium(II) intermediate **23** is often considered as a sp^2-hybridised electrophile equivalent, able to undergo reaction with a nucleophilic equivalent (Scheme 6).



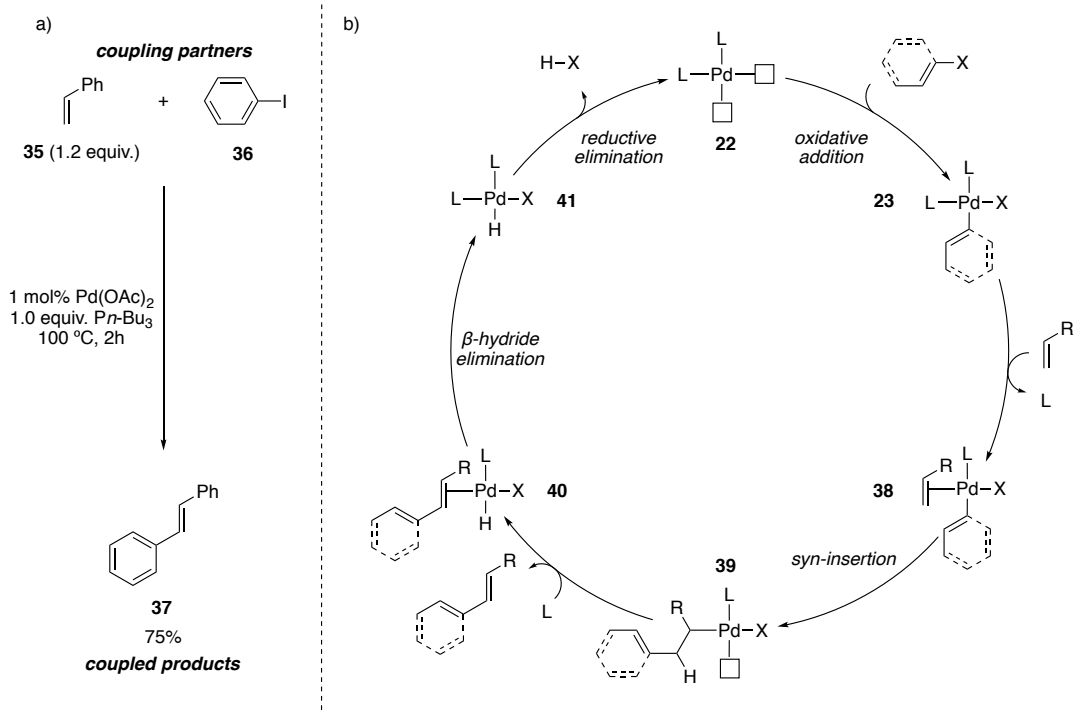
Scheme 6 – Palladium(II) intermediates as sp^2 electrophile equivalents

Significant interest has been invested in the use of heteroatomic nucleophiles to attack aryl/alkenyl-palladium(II) intermediate **23**. The first and most famous of these processes is the Buchwald-Hartwig reaction, which directly couples free amines to the *in situ*-formed sp^2 electrophile equivalent (Scheme 7).[18,19] The reaction typically requires a strong base, sterically demanding ligands and elevated temperatures and has evolved to tolerate a wide range of nitrogen-bearing inter- and intramolecular coupling partners.[20,21] The analogous use of oxygen,[22] sulfur[23] and phosphorous[24] nucleophiles has also been reported.



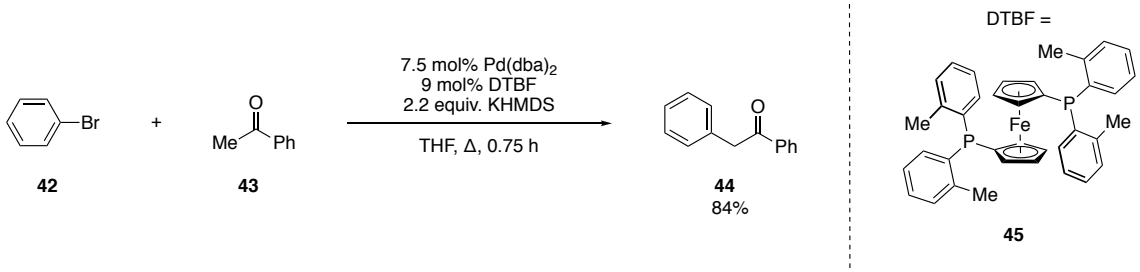
Scheme 7 – a) Hartwig's,[19] and b) Buchwald's[18] original amine coupling conditions

Similarly, the reaction of carbon-based functional groups with aryl/alkenyl-palladium(II)-intermediates has also been widely exploited. One of the most important of such processes is the alkene-coupling Mizoroki-Heck reaction (Scheme 8), which proceeds by a distinct mechanism to the general cross-coupling procedure described above.[25–27] In this reaction, following oxidative addition, palladium complex **23** undergoes ligand exchange to give alkene-bound adduct **38**. The aryl/alkenyl moiety inserts into the alkene to generate coordinatively-unsaturated alkyl palladium(II) intermediate **39**, which then undergoes β-hydride elimination to give the coupled alkene-bound palladium hydride **40**. Ligand exchange and reductive elimination then occur to furnish the functionalised alkene product, an equivalent of acid and the regenerated catalyst.



Scheme 8 – a) Heck reaction;[25] b) Heck reaction mechanism (L = phosphine)[27]

As there is substantial back-bonding from the palladium centre to the alkene in olefin-bound complex **38**,[28,29] it cannot be claimed that the alkene component in the Mizoroki-Heck reaction acts as a true nucleophile. However, there is less ambiguity with the use of enolates to nucleophilically attack aryl- and alkenyl-palladium(II) intermediates.[30–36] One such enolate arylation process, Hartwig's α-arylation of methyl/phenyl ketone, is shown below (Scheme 9). [31]

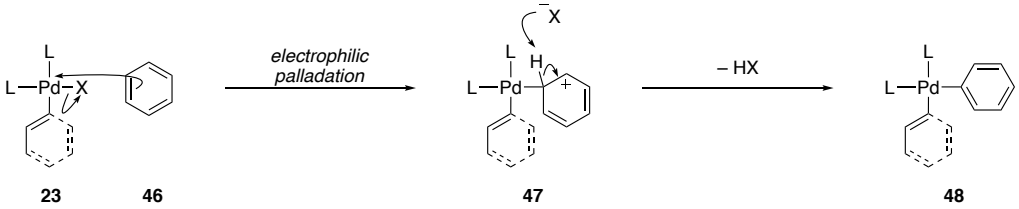


Scheme 9 – Hartwig's ketone α-arylation *via* enolate formation[31]

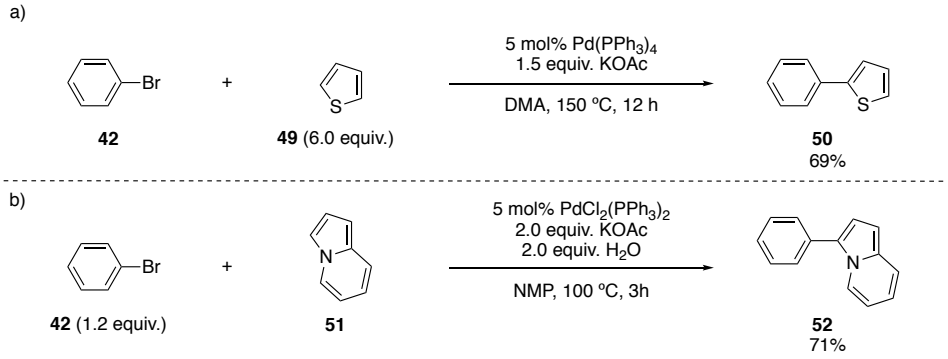
1.2.2. Electrophilic metalation of arenes with aryl/alkenyl-palladium(II) species

The use of carbon-based nucleophiles to attack *in situ*-generated sp^2-electrophile equivalents has been extended to Friedel-Crafts chemistry, allowing the coupling of arenes to alkenyl/aryl-halides *via* a C–H functionalisation approach (Scheme 10). Such a procedure advantageously removes the need for pre-functionalisation of the aryl group (by borylation, metalation, *etc.*).[37] The use of electron-rich heterocycles has been particularly successful under this C–H activation manifold. Friedel-Crafts-selective

functionalisation is observed on the exposure of (benzo)thiophenes, (benzo)furans and nitrogenous heteroaromatics to the combination of aryl/vinyl halides and a palladium source (Scheme 11).[38–41]

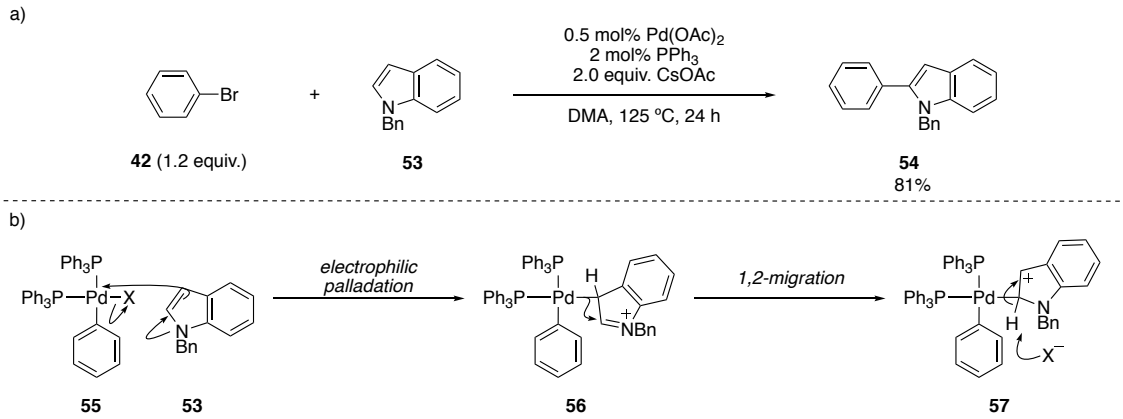


Scheme 10 – Direct electrophilic palladation *via* a Friedel-Crafts type process



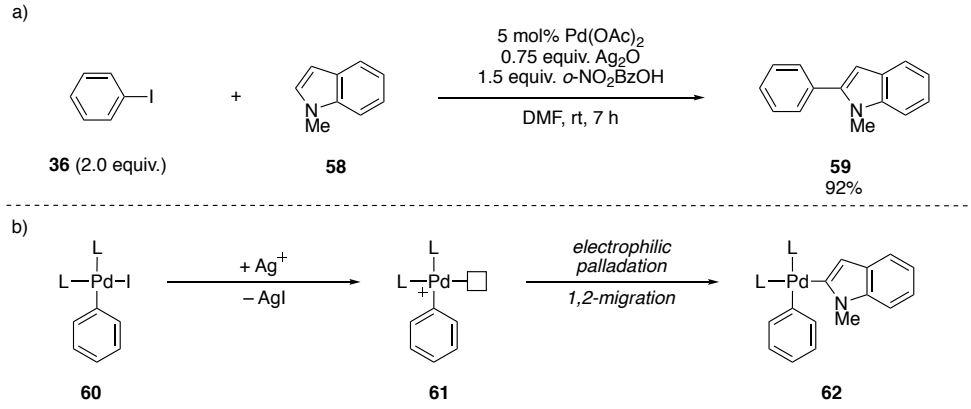
Scheme 11 – Representative palladium-catalysed Friedel-Crafts type reactions proceeding through a palladium(II)–aryl intermediate: a) Ohta's thiophene arylation[38] and b) Gevorgyan's indolizine arylation[40]

Interestingly, Sames first demonstrated that C-2 arylation results on the addition of indoles to reaction conditions that generate electrophilic aryl-palladium(II) intermediates (Scheme 12a).[42] This unexpected selectivity derives from a Friedel-Crafts C-3 palladation followed by a 1,2-migration to give C-2 palladated intermediate **57** for elimination then reductive elimination (Scheme 12b). The metalation/migration pathway was evidenced by the observation of a large secondary kinetic isotope effect at the indole C-3 position (k_H/k_D = 1.6) and by Hammett investigations varying the indole at the C-7 position. The C-2 selectivity can be overturned with free N–H indoles by using magnesium bases.[43]



Scheme 12 – Sames' C-2 indole arylation a) procedure[42] and b) key palladation/migration mechanism[43]

The forcing conditions required to effect the electrophilic metalation reactions shown in Schemes 11 and 12 is attributable to the strongly electron-donating ligand-field of the palladium–aryl adduct **55**, reducing the electrophilicity of the metal centre. Larrosa sought to overcome the use of such extreme conditions for the palladium-catalysed arylation of indole **58** by removing phosphine ligands and adding a silver salt to the reaction mixture (Scheme 13a). According to Larrosa's hypothesis, the absence of stabilising phosphines and the abstraction of iodide ligands by the silver salt would give formally cationic aryl-palladium(II) intermediate **61**. The electron-deficiency of this complex was expected to promote electrophilic metalation, allowing the reaction to proceed at room temperature (Scheme 13b).

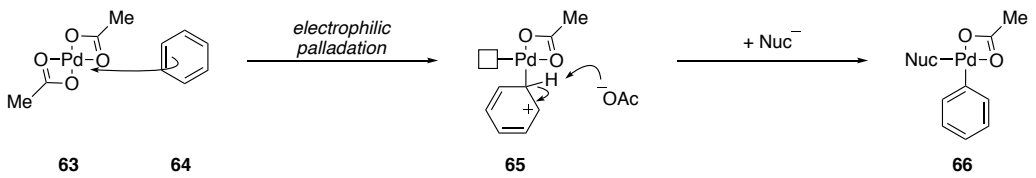


Scheme 13 – Larrosa's C-2 indole arylation a) procedure and b) conceptual mechanistic overview[44]

Despite the clear efficacy of this process, it is not immediately clear how the palladium(II) source introduced at the start of the reaction is reduced to palladium(0). Such a reduction process is required for an initial oxidative addition step that furnishes **60**. It is therefore possible that the reaction proceeds by a distinct mechanism to that proposed by Larrosa, likely by the pathway discussed in the next section.

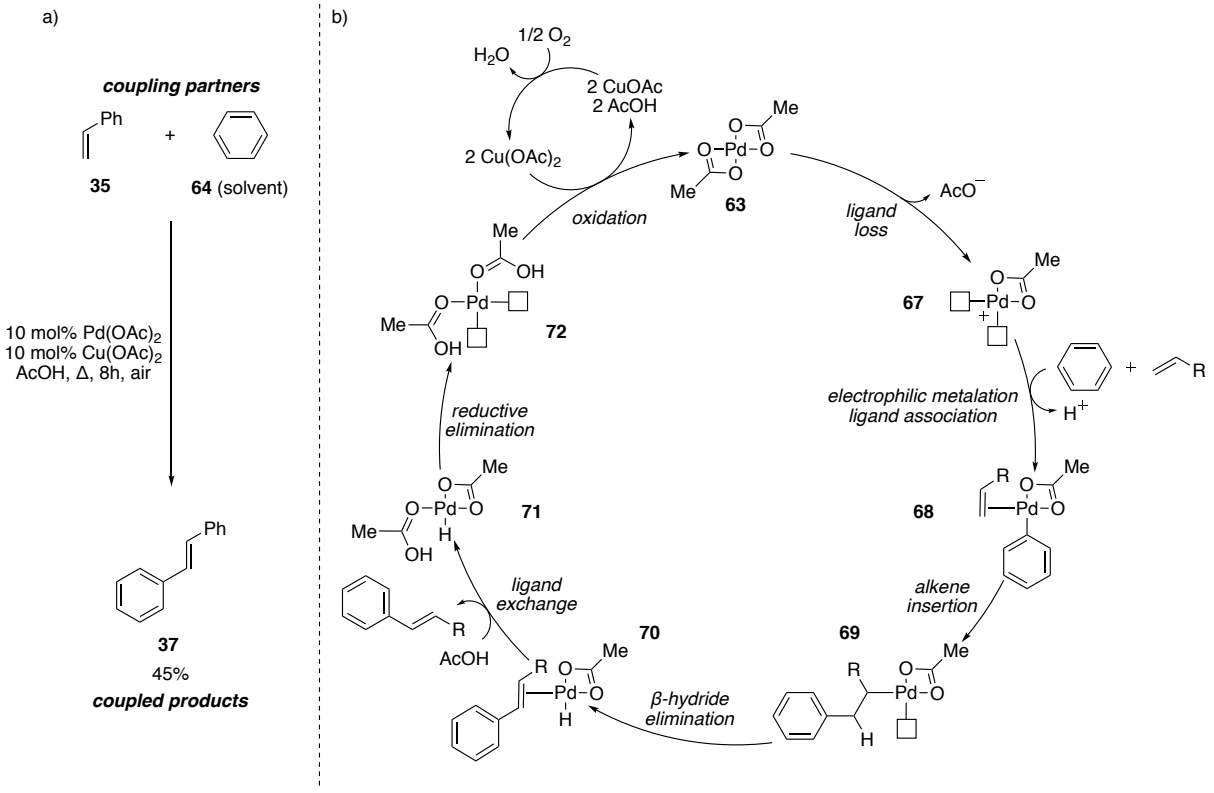
1.2.3. Direct electrophilic metalation of nucleophilic arenes

An alternative strategy for the generation of palladium(II)-centred electrophilic arene equivalents requires no phosphine ligand or aryl/alkenyl(pseudo)halide. Reactivity proceeds *via* the direct electrophilic palladation of a nucleophilic arene with an unstabilised palladium(II) source, resulting in the generation of an electrophilic arene equivalent. Subsequent nucleophilic attack of the aryl-palladium(II) species furnishes palladium complex **66** for reductive elimination (Scheme 14).



Scheme 14 – Alternative electrophilic metalation approach employing palladium (II) salts as the electrophile

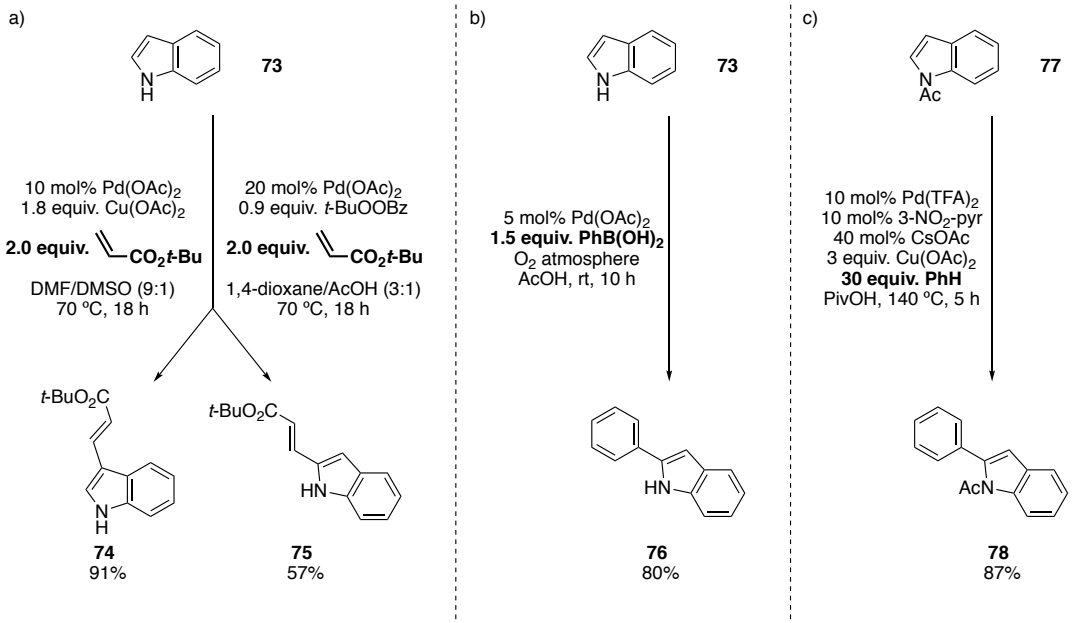
Fujiwara first explored such reactivity in his seminal 1967 work detailing the coupling of simple arenes with alkenes to form styrene derivatives (Scheme 15).[45–49] The reaction is proposed to begin with the loss of an acetate ligand from palladium(II) acetate.[49] An aryl group then undergoes electrophilic metalation with cationic palladium(II) complex **67** with the resulting complex then bound by an alkene to give **68**. A Heck-type mechanism of alkene insertion and β-hydride elimination then follows to furnish product-bound palladium hydride intermediate **70**. Ligand exchange and reductive elimination processes then furnish the product and a Pd(0) complex. The low-valent palladium is then re-oxidised to palladium(II) acetate by copper(II) acetate under aerobic conditions. As can be seen from the use of benzene in the reaction, this Pd(II)/Pd(0) manifold is able to functionalise relatively non-nucleophilic arenes under milder conditions than many of the Pd(0)/Pd(II) procedures described above (Schemes 11 and 12). Fujiwara's alkenylative Friedel-Crafts C–H activation procedure has been extended to substituted benzene rings and various heterocycles.[50,51]



Scheme 15 – Fujiwara's oxidative Heck a) process and b) mechanism[45–47]

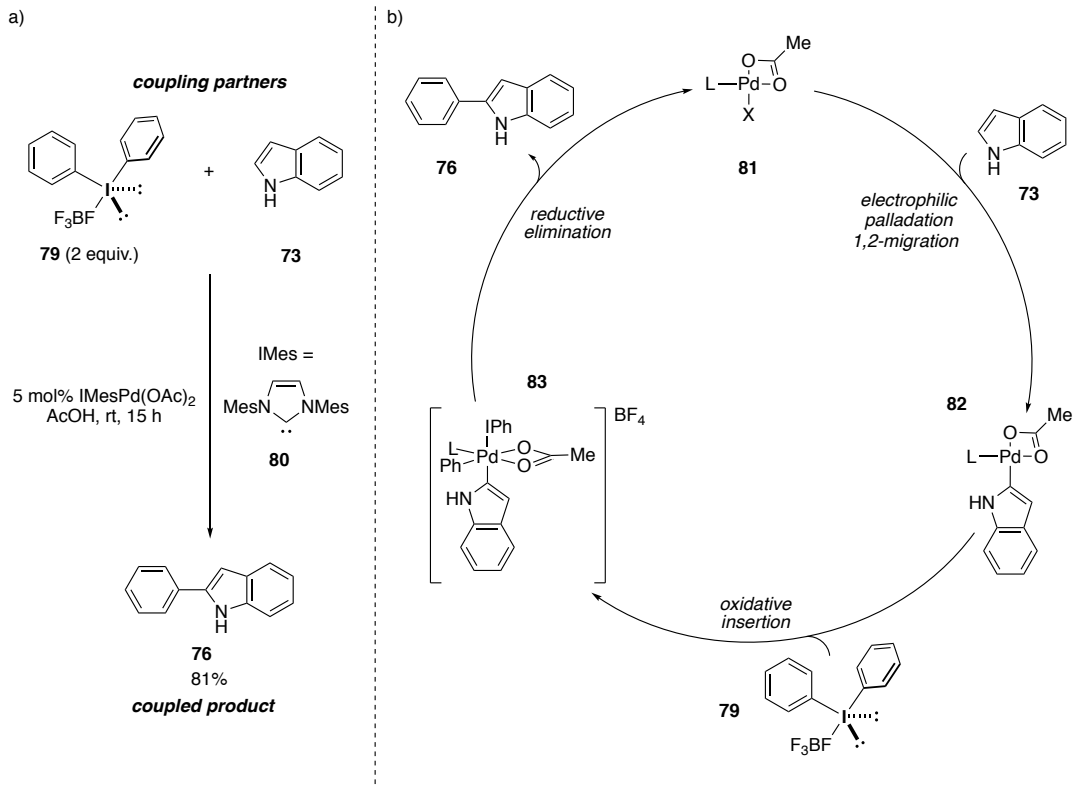
The palladium(II)-palladium(0) cycling approach has been modified by a number of groups towards the functionalisation of indoles using different nucleophile coupling strategies (Scheme 16). Gaunt's indole alkenylation achieves selective C-2/C-3 functionalisation with a judicious choice of solvent and oxidant.[52] Shi effected an oxidative Suzuki coupling, intercepting the aryl-palladium(II) intermediate with a boronic acid to furnish 2-arylated indoles.[53] Finally, Fagnou employed concerted-metalation-

deprotonation chemistry[54–56] as a secondary C–H activation mode to transfer an additional unfunctionalised arene to the electrophilically-palladated palladium(II) intermediate.[57]



Scheme 16 – a) Gaunt's indole C-2/C-3 selective oxidative Heck reaction,[52] b) Shi's oxidative Suzuki coupling with indole,[53] c) Fagnou's dual C–H activation indole phenylation procedure[57]

Sanford also employed the intrinsic electrophilicity of palladium(II) acetate in her 2006 indole arylation employing a diaryliodonium salt and using a palladium(II)-palladium(IV) redox manifold (Scheme 17a).[58] The reaction is proposed to proceed through the electrophilic metalation and 1,2-migration of indole **73** with palladium(II) acetate species **81** before the resulting adduct (**82**) undergoes oxidative addition with diaryliodonium salt **79**. Reductive elimination of diarylated palladium(IV) intermediate **83** gives the coupled product and re-generates the palladium(II) catalyst (Scheme 17b).

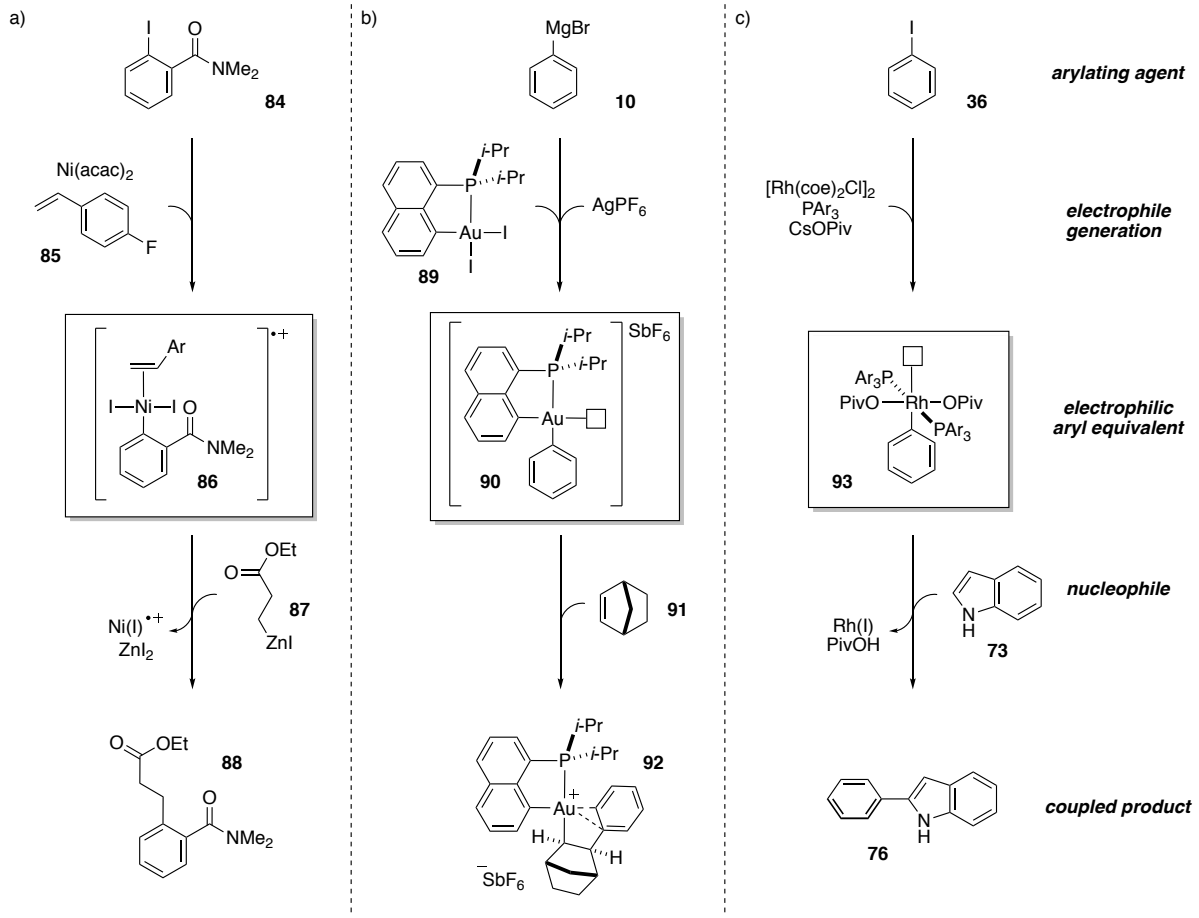


Scheme 17 – Sanford's Pd(II)/Pd(IV) C-2 indole arylation a) process and b) mechanism[58]

1.3 Generation of sp² Electrophile Equivalents with Other Metals

The generation and reactivity of electrophilic sp² equivalents has also been described with metals other than palladium. Although the chemistry of such processes is generally less well-understood than the analogous palladium-catalysed methods, this area of research is expanding rapidly. Three examples are shown below (Scheme 18).

The first of these processes (Scheme 18a) is a Nickel-catalysed Negishi reaction.[59] Although the mechanism of this reaction is poorly described, it has been evidenced that the key electrophilic intermediate is nickel(III) radical cation **86**.[60] Transmetalation of **86** with alkyl zinc **87** and subsequent reductive elimination provides the alkyl-coupled product. Separately, Miqueu, Amgoune and Bourissou have demonstrated phenylmagnesium bromide **10** to react with gold(III) complex **89** to give the cationic aryl-gold(III) complex **90** (Scheme 18b).[61] This species is observed to react with alkenes to give unusual gold(III)-arene adducts. Finally, Sames has demonstrated electrophilic aryl-rhodium(III) complexes to functionalise indoles at the C-2 position (Scheme 18c).[62] Interestingly, in contrast with the behaviour observed under palladium catalysis (Scheme 12), the rhodium-catalysed procedure is evidenced to occur through a concerted metalation-deprotonation pathway to directly furnish the C-2 arylated product **76**.



Scheme 18 – a) Knochel's nickel-catalysed Negishi coupling with alkyl zinc reagent **87**;[59] b) Miqueu, Amgoune and Bourissou's generation of gold(III) arene complex **90**;[61] c) Sames' rhodium-catalysed indole C-2 arylation proceeding through a CMD process[62]

Much attention has been directed towards the reactivity of aryl- and alkenyl copper(III) species as potent sp^2-hybridised electrophile equivalents. The reason for this interest can be seen by comparing a copper(III) complex with its palladium(II) analogue (Figure 3). As d^8 metal ions, both species would have 16-electron configurations and a square-planar structure. However, the first-row d-block position of copper and the increased charge on the metal centre indicates that the Cu(III) species will be substantially more electrophilic than the Pd(II) complex. It was predicted that the copper(III) species would demonstrate functionalisation chemistry different to that observed with palladium. The following section discusses the generation and reactivity of copper(III) intermediates in catalysis.

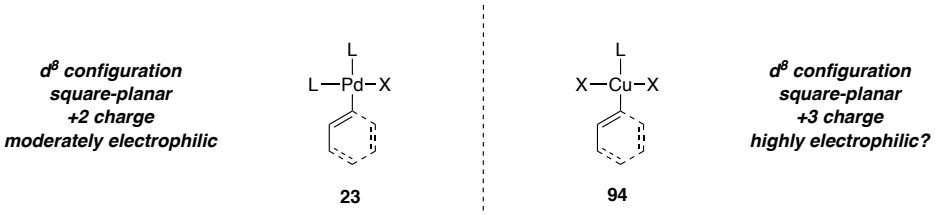


Figure 3 – Comparison of aryl/alkenyl-Pd(II) and aryl/alkenyl-Cu(III) species

1.4 The Generation and Reactivity of Copper(III) Species

1.4.1. Copper(III) intermediates in synthetic chemistry

Although copper(III) species were first proposed as early as 1974,[63] the first unambiguous evidence for such adducts was not provided until the late 1980s, achieved by the crystallographic characterisation of a number of stabilised Cu(III) complexes (Figure 4).[64–66]

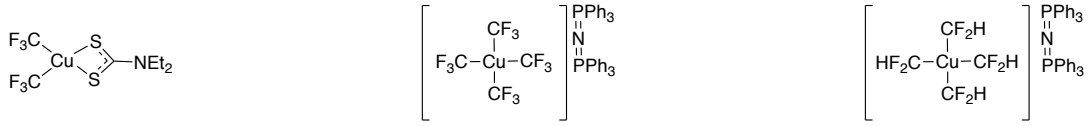
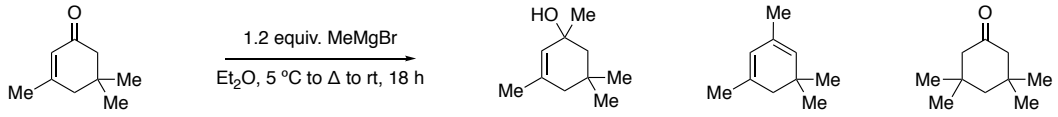


Figure 4 – Examples of crystallographically characterised organo-copper (III) species[64–66]

Copper(III) species are increasingly implicated in important methods in organic chemistry.[67] Possibly the best known of such a reaction is the copper catalysed conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds, first described by Kharasch in 1941. In this study, the addition of catalytic copper(I) chloride to the reaction between methylmagnesium bromide and isopherone was observed to overturn the natural 1,2-regioselectivity of the Grignard addition (Table 1).[68]

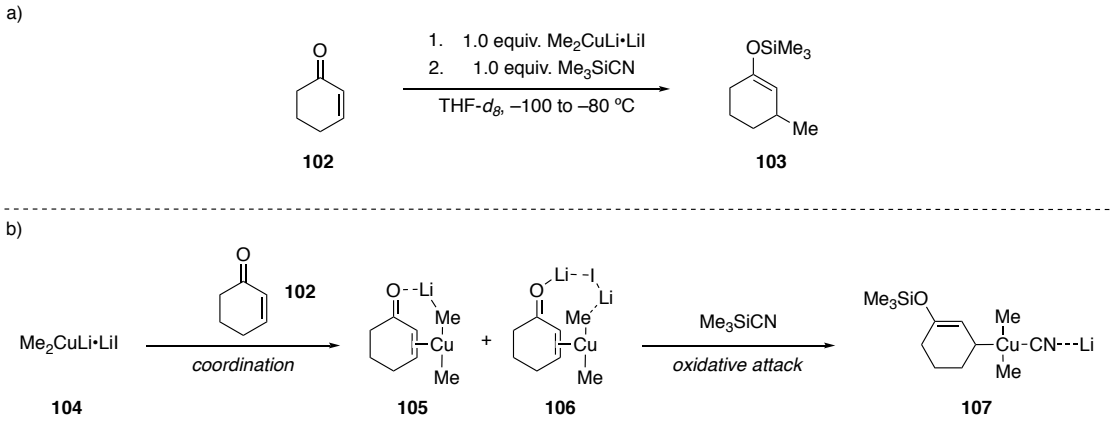


Entry	Additive	Yield/ %		
		99	**100**	**101**
1	-	43	48	-
2	1 mol% CuCl	-	7	83

Table 1 – Addition of methylmagnesium bromide to isopherone (**98**) in the presence and absence of copper chloride[68]

The related addition of Gilman reagent **104** to cyclohexanone (Scheme 19a) has been investigated both with rapid-injection nuclear magnetic resonance (NMR) spectroscopy and computational methods.[69,70] These studies enabled the characterisation of the intermediate copper(I) and copper(III) species on-path towards the production of conjugate adduct **103** (Scheme 19b). It was determined that the mechanism initially proceeds by the coordination of Gilman reagent **104** to the enone to furnish adducts **105** and

106. Addition of trimethylsilylcyanide results in the oxidative attack of the copper(I) centre to the conjugate position of the Michael acceptor, thereby generating copper(III) adduct **107**. The production of **107** is in line with previous computational studies that indicate trialkyl, square-planar, anionic Cu(III) species to be particularly stable.[71,72] **107** undergoes a formal reductive elimination on warming to give the coupled product **103**.

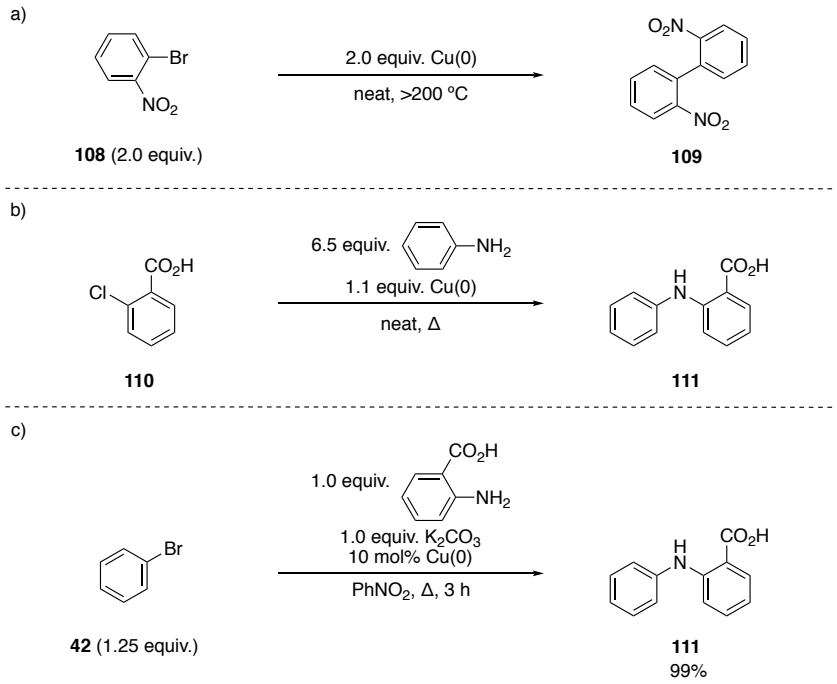


Scheme 19 – a) Overview of the addition of Gilman reagent **104** to cylohexenone and b) spectroscopically determined copper-centred intermediates on this pathway[69]

Although these conjugate addition studies show the accessibility of copper(III) species, the chemistry observed more reflects the reducing ability of copper(I) species rather than the electrophilicity of Cu(III). However, the reactivity of catalytically-generated, copper-centred sp^2-hybridised electrophile equivalents is implicated in another historically-important process: the Ullmann reaction.

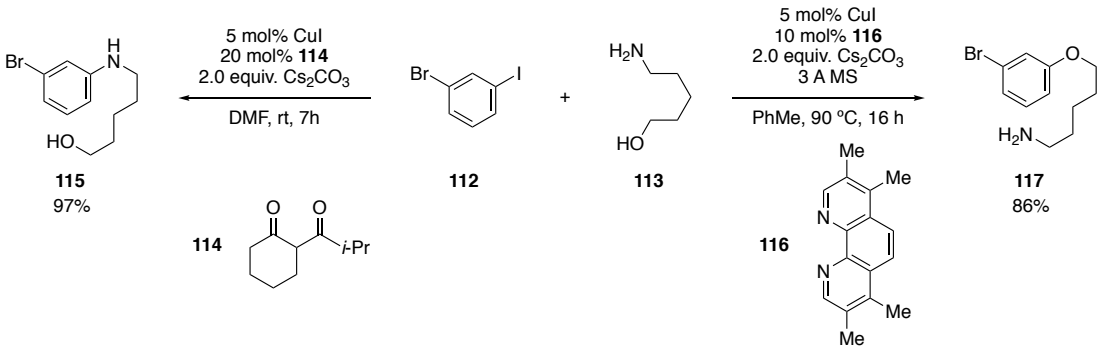
1.4.2. Generation of electrophilic Cu(III) intermediates in Ullmann-type reactions

Ullmann's investigations represent some of the earliest work carried out in cross-coupling. His studies focused on the use of copper to mediate *ipso*-reactivity with aryl-halides. The first of his developments was described in 1901 and details the homocoupling of *ortho*-nitrobromobenzene (Scheme 20a).[73] An analogous amination procedure was described two years later, coupling aniline to *ortho*-chlorobenzoic acid **110** (Scheme 20b).[74] This amination process was further developed in 1906 by Goldberg, demonstrating that catalytic loadings of copper could give high product yields on addition to a basified mixture of bromobenzene and *ortho*-aminobenzoic acid in refluxing nitrobenzene (Scheme 20c).[75]



Scheme 20 – a) Ullmann's copper(0)-mediated biaryl formation;[73] b) Ullmann's copper(0)-mediated amination procedure;[74] Goldberg's copper(0)-catalysed amination procedure[75]

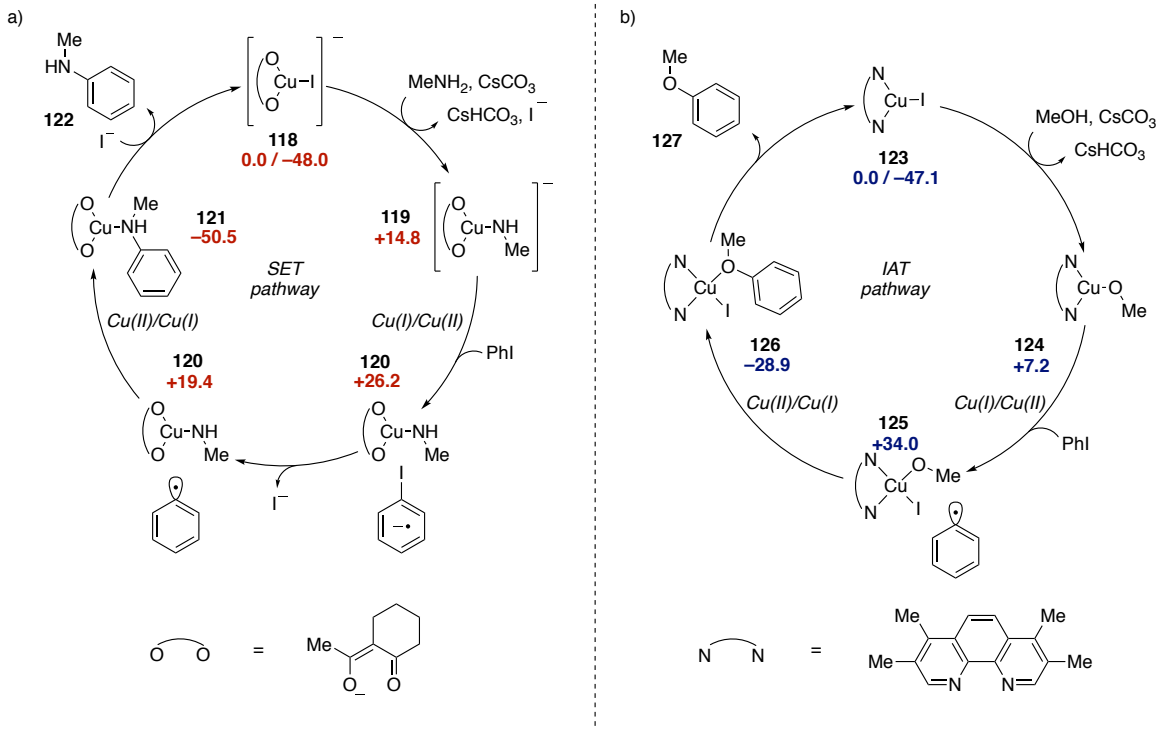
The extreme conditions required for Ullmann and Goldberg's processes meant that the use of copper catalysis for cross-coupling was comparatively under-researched for the next century.[67,76] However, in 2001 and 2002, the Taillefer and Buchwald groups concurrently patented Ullmann-type processes employing ligands to enhance reactivity.[77–79] These studies prompted a revival in the area and led to the development of a large number of carbon-heteroatom bond-forming processes.[80,81] One such example can be seen in Buchwald's *N*-/*O*-selective arylation of aminoalcohols, where the selective coupling of either the alcohol or amine portion of **113** is controlled by the ligand employed (Scheme 21).[82] Diketone ligand **114** gives amine functionalisation, whilst the use of phenanthroline **116** leads to reaction through the alcohol. Whilst the differing chemoselectivity can be explained based on the native ligand charge and pKa differences, the wider mechanism of the process is disputed.



Scheme 21 – Buchwald's *N*-/*O*-selective arylation of aminoalcohols[82]

There are two generally proposed pathways for Ullmann-type reactivity. One such proposal invokes a Cu(I)-Cu(II) cycling mechanism and radical behaviour, whilst the second focuses on a Cu(I)-Cu(III) redox loop and employs oxidative addition and reductive elimination steps. Extensive kinetic investigations have been carried out to either confirm or disprove either of these mechanisms, but have yielded few conclusive results. Studies employing radical traps and radical clocks have, with the exception of a photoinduced process,[83] demonstrated free-radical activity to not be mechanistically viable.[84–86] These results can be rationalised by any radical activity occurring in a closed-shell manner but can also be taken as evidence for a Cu(I)/Cu(III) cycle. Unfortunately, this latter manifold has also proved very difficult to experimentally support, largely due the identification of the aryl-halide activation step as the turnover-limiting step in Ullmann couplings. Computational evaluation has therefore become the method of choice for the investigation of the behaviour of copper-catalysed heteroatom arylation reactions using iodoarenes.

Computational studies have been carried out on Buchwald's *N*-/*O*-selective aminoalcohol arylation process (Scheme 21). In line with the disagreement regarding the behaviour of the copper catalyst, both Cu(I)-Cu(II) and Cu(I)-Cu(III) redox cycles have been investigated. Firstly, computing model systems with methanol and methylamine, Houk and Buchwald proposed distinct closed-shell radical mechanisms for *N*- and *O*-arylation (Scheme 22).[87]

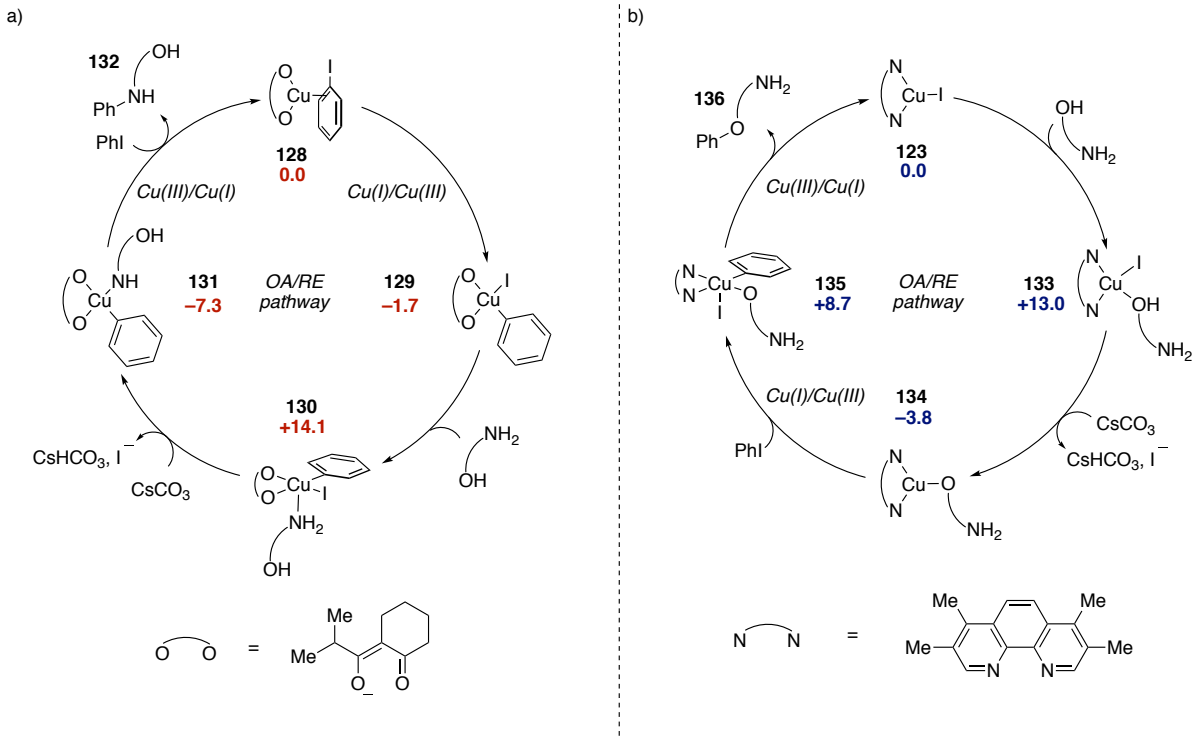


Scheme 22 – Houk and Buchwald's a) SET and b) IAT mechanistic rationale;[87] bold red/blue quantities denote the relative energy of the system at that stage of the mechanism (kcal mol^{-1})

N-arylation was computed to proceed through a single electron transfer (SET) process with the catalyst resting state the anionic ligand-bound copper(I) iodide adduct **118** (Scheme 22a). The first step of the reaction involves the displacement of the iodide with deprotonated amine, giving anionic copper(I) amide **119**. This species then acts as a single-electron reductant, reducing iodobenzene to its corresponding radical anion and furnishing the copper(II) adduct **120**. The radical anion then loses iodide to give a phenyl radical which rapidly attacks the copper-bound nitrogen to generate copper(I) amine complex **121**. Displacement of the coupled amine with iodide regenerates the anionic adduct **118**.

In contrast, *O*-arylation was determined to occur through an iodine atom transfer (IAT) mechanism (Scheme 22b). In this process, methanol displaces iodide from the neutral copper(I) species **123** and is concurrently deprotonated to give copper(I) methoxide **124**. The intermediate then undergoes iodine atom transfer to give copper(II) intermediate **125** and phenyl radical. The radical then attacks the bound methoxide, formally reducing the copper centre to generate ether-bound copper(I) iodide **126**. Dissociation of the product aryl ether regenerates the catalyst.

Computing the reaction system employing the true substrate, the Fu group proposed alternative mechanisms for the observed *N*- and *O*-arylations (Scheme 23).[88] Both of these processes proceed through a copper(I)/(III) redox manifold.



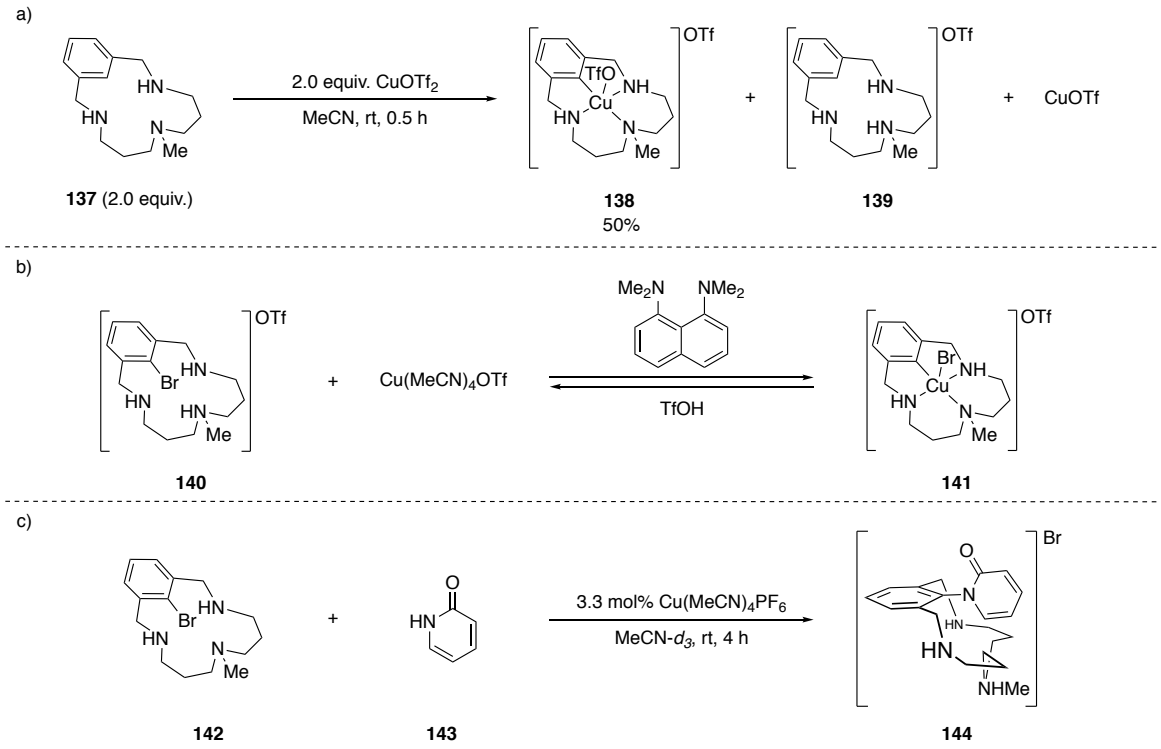
Scheme 23 – Yu's a) nitrogen arylation and b) oxygen arylation with a Cu(I)/Cu(III) mechanistic rational;.[88] bold red/blue quantities denote the relative energy of the system at that stage of the mechanism (kcal mol^{-1})

In the case of nitrogen arylation (Scheme 23a), the catalytic cycle rests at the copper(I)-aryl iodide adduct **128**. Oxidative addition of **128** is observed to be relatively energetically favourable ($\Delta G^{\ddagger}$ = +9.7 kcal mol^{-1}), giving copper(III) intermediate **129**. A rate-determining apical association of the aminoalcohol then gives nitrogen-bound adduct **130** (ΔG = +14.1 kcal mol^{-1}). Subsequent elimination of iodide and concurrent deprotonation of the amine gives Cu(III) amide **131**, which then undergoes reductive elimination to furnish the nitrogen-coupled adduct **132** and regenerate copper(I).

Oxygen arylation (Scheme 23b) proceeds from copper(I) iodide complex **123**. Ligand association with the hydroxylamine gives metastable intermediate **133**, which rapidly loses iodide with deprotonation of the alcohol to form copper(I) alkoxide **134**. The *oxy*-anion-bound intermediate then undergoes the rate-limiting oxidative addition step ($\Delta G^{\ddagger}$ = 22.7 kcal mol^{-1}), giving apical-iodide bound Cu(III) adduct **135**. Reductive elimination furnishes the coupled product **136** and reforms the Cu(I) iodide catalyst.

Yu has also calculated the highest-energy points on Houk and Buchwald's SET/IAT models when applied to the use of 5-amino-pentan-1-ol **113**. It is shown that for nitrogen arylation, the highest point on the oxidative addition/reductive elimination energetic profile is substantially lower in energy than for the proposed SET pathway ($\Delta\Delta G^{\ddagger}$ = 34.8 kcal mol^{-1}). Similarly, the highest point on the Cu(I)/Cu(III) pathway towards oxygen arylation is lower in energy than that of the IAT mechanism ($\Delta\Delta G^{\ddagger}$ > 16.2 kcal mol^{-1}). These data indicate that a copper(I)-copper(III) cycling mechanism is generally more favourable than copper(I)-copper(II) radical processes.

Further support for a copper(I)-copper(III) reaction manifold can be seen in Ribas' work on the generation and reaction of crystallographically characterised aryl-copper(III) adducts.[89] Ribas' crucial work builds on results published in 2002 from a collaboration between Hedman, Hodgson, Llobet and Stack.[90] These early studies detail the generation of copper(III)-aryl adducts *via* disproportionation from copper(II) salts in the presence of triazamacrocylic ligand **137** (Scheme 24a). The products were verified by X-ray crystallography and the oxidation state of the metal centre was confirmed by K-edge absorption spectroscopy. Using an engineered ligand backbone (**140**) and basic conditions, Ribas directly demonstrated oxidative addition of copper(I) salts into C–Br bonds to occur (Scheme 24b), allowing the production of stable copper(III) adducts (**141**). Interestingly, the reaction could be reversed on the addition of acid to the system. Furthermore, macrocylic aryl bromide **142** has been observed to undergo coupling with nucleophile **143** in the presence of catalytic copper hexafluorophosphate (Scheme 24c), firmly supporting the role of Cu(III) in the Ullmann reaction. This result was reinforced by the production of aryl ethers on the exposure of copper(III) species such as **138** and **141** to oxygen nucleophiles.[91]

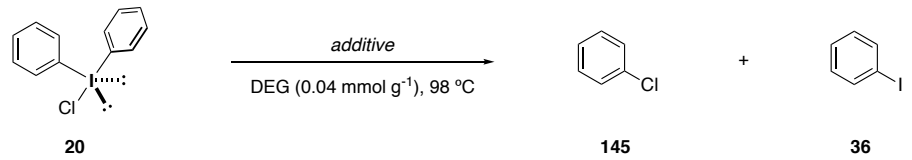


Scheme 24 – a) Hedman, Hodgson, Llobet and Stack's product of copper(III)-aryl species by copper(II) disproportionation;[90] Ribas' b) reversible Cu(I) oxidative addition into aryl bromide **140** and c) catalytic coupling of **142** to nucleophile **143**[89]

Whilst other mechanistic pathways cannot be discounted, clear evidence has been provided to indicate that copper(I)-copper(III) redox cycling is possible. The accessibility of Cu(III) under this reaction manifold has implications beyond the Ullmann reaction as other processes have also been proposed to proceed through high-valent copper intermediates. Examples include the Hurtley reaction,[92–94] the Chan-Lam coupling,[95] and the aromatic Finkelstein reaction.[96] Finally, the mechanistic studies carried out on the reactivity of copper salts with aryl halides has allowed understanding of copper-catalysed reactions employing diaryliodonium salts, the focus of the remainder of this chapter.

1.4.3. Generation and reactivity of electrophilic Cu(III) species with iodonium salts

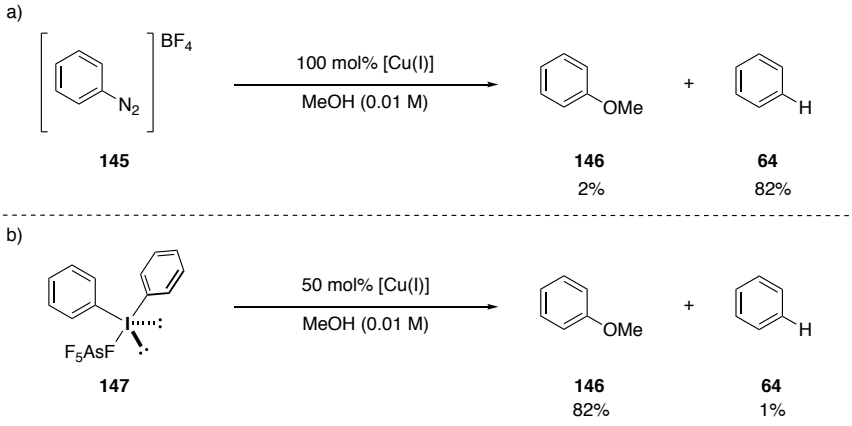
The ability of copper salts to catalyse reactions with iodonium salts was first described by Beringer in 1956. It was noted that the addition of 0.1 mol% copper chloride to a solution of diphenyliodonium chloride **20** accelerated the maximum rate of iodane decomposition by a factor of 25 (Table 2).[97] Interestingly, although the maximal rate of decomposition was similar with both copper(I) and copper(II) salts (entries 2 and 3), copper(I) appears to be the active catalyst in the reaction as the use of copper(II) chloride demonstrates an induction period. This hypothesis was further supported by Lockhart's observation of a significant rate inhibition on the addition of the Cu(I)-chelating ligand cuproin to an analogous reaction.[98,99]



Entry	Additive	k_1 (max) / h^{-1}
1	-	0.021
2	0.1 mol% $CuCl_2$	0.49
3	0.1 mol% CuCl	0.52

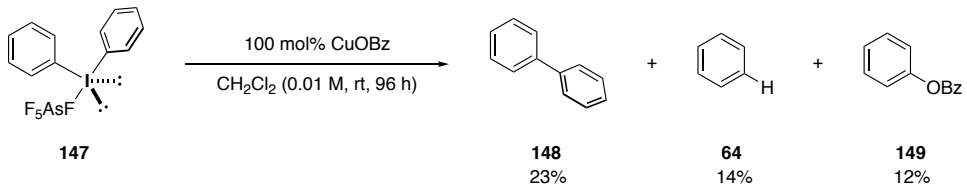
Table 2 –Beringer's observation of an increased demcomposition rate on the addition of copper salts to a solution of diaryliodonium salt **20** [97]

Further investigating the reactivity of diaryliodonium salts with copper, Lockhart compared the behaviour of diazonium and diaryliodium salts on exposure to a copper(I) source in methanol solution. Whilst the decomposition of the diazonium salt was observed to dominantly furnish benzene, the analogous reaction with iodonium salt **147** gave majority anisole production (Scheme 25). These results imply the former reaction to proceed *via* free-radical chemistry and the latter to proceed through a distinct mechanistic pathway, disfavouring Roberts' hypothesis of a radical process for the copper-catalysed decomposition of diaryliodonium salts.[100]



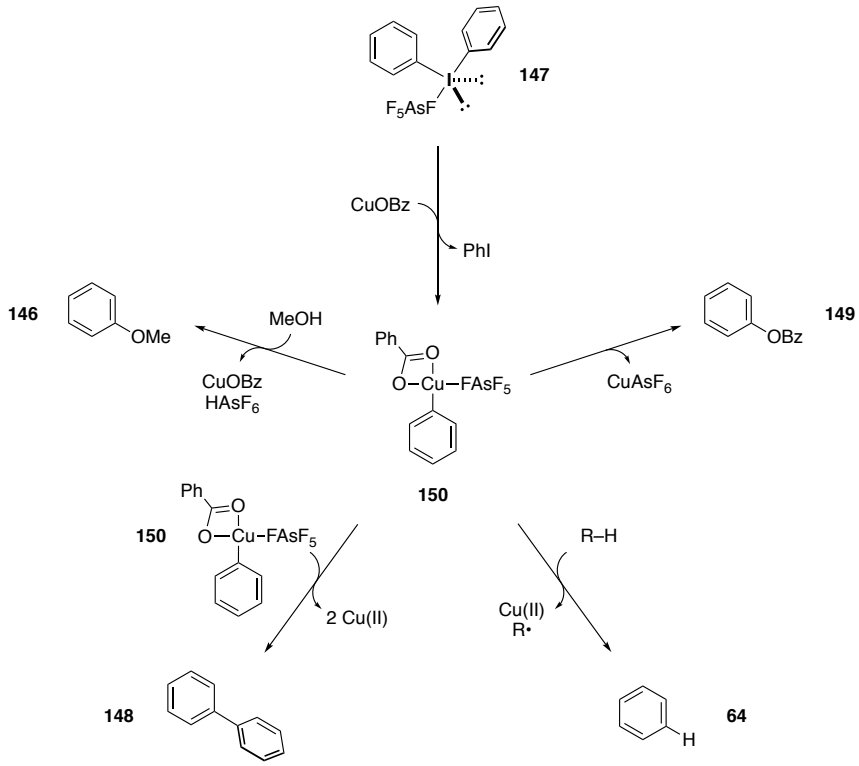
Scheme 25 – Comparison between the decomposition of a) diazonium salt **145** and b) diaryliodonium salt **147**

However, treatment of **147** with copper(I) benzoate in dichloromethane furnished a mixture of benzene, biphenyl and phenyl benzoate (**149**), behaviour more consistent with radical activity (Scheme 26). The relative amount of biphenyl produced was observed to be proportional to the copper loading, implying a bimolecular reaction in copper for the generation of this species.



Scheme 26 – Reaction of diphenyliodonium hexafluoroarsenate with catalytic copper in dichloromethane[98]

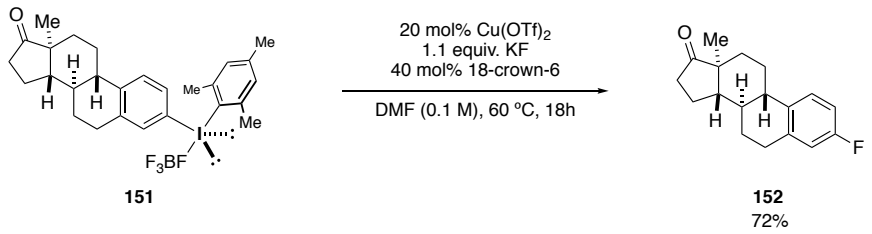
Lockhart noted that all the observed products of the copper-catalysed decomposition of **147** could be rationalised through the intermediacy of copper(III) species **150** (Scheme 27). Anisole **146** and phenyl benzoate **149** can be generated by nucleophilic attack/reductive elimination of **150**. Biphenyl **148** is proposed to result from reaction of the high-valent intermediate with a second equivalent of the copper(III) species. Finally, the production of benzene can be attributed to a minor radical decomposition process, abstracting a hydrogen atom from the reaction medium.



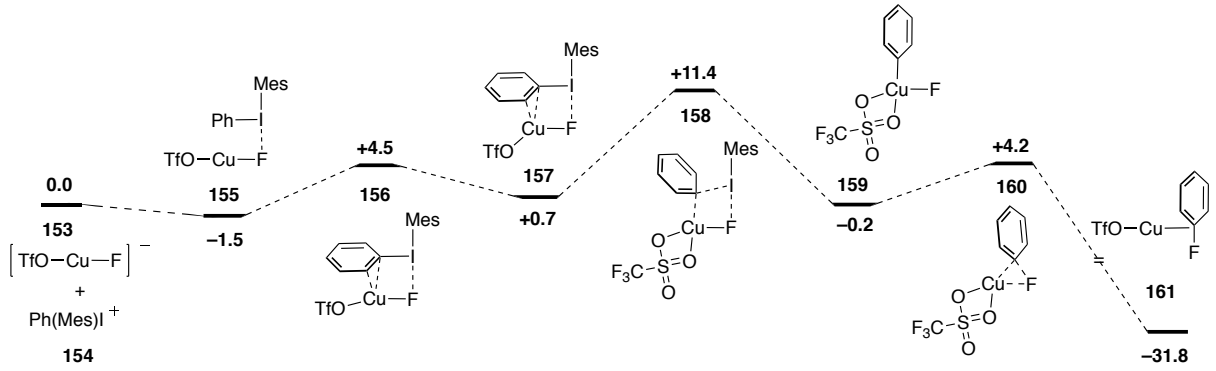
Scheme 27 – Lockhart's Cu(III) hypothesis rationalising all observed products[98]

Canty and Sanford have recently demonstrated the mechanistic role of a copper(III) intermediate in their procedure for the generation of aryl fluorides from diaryliodonium salts and KF (Scheme 28).[101] Computational investigations on the fluorination of phenyl(mesityl)iodonium triflate (Scheme 29), revealed that the first step in the reaction was the association of anionic copper adduct **153** with free iodonium cation **154**. The resulting copper-iodonium adduct **155** then rearranges to π-bound copper intermediate **157** before oxidative insertion occurs with a low energetic penalty *via* transition state

structure **158**. κ²-Stabilised aryl-copper(III) species **159** then undergoes facile reductive elimination to furnish fluoroarene-bound copper(I) species **161**. Dissociation of fluorobenzene and association of a fluoride allows for catalyst turnover.



Scheme 28 – Canty and Sanford's diaryliodonium fluorination procedure[101]



Scheme 29 – Canty and Sanford's computation investigation of their fluorination procedure; energies are given as ΔG relative to the starting system in kcal mol-1 [101]

Canty and Sanford have since detailed three other possible oxidative addition transition states for their fluorination process (Figure 5).[102] Difluorinated copper(I) adduct **163** appears to have to the lowest-energy oxidative addition barrier.

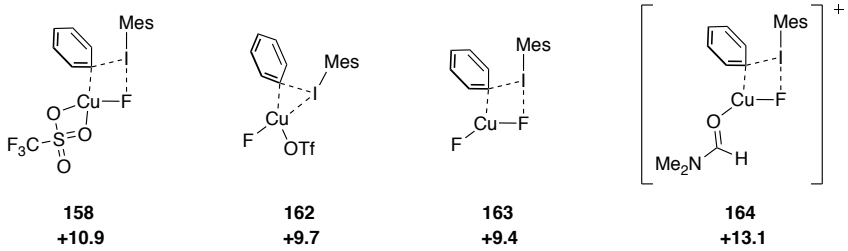
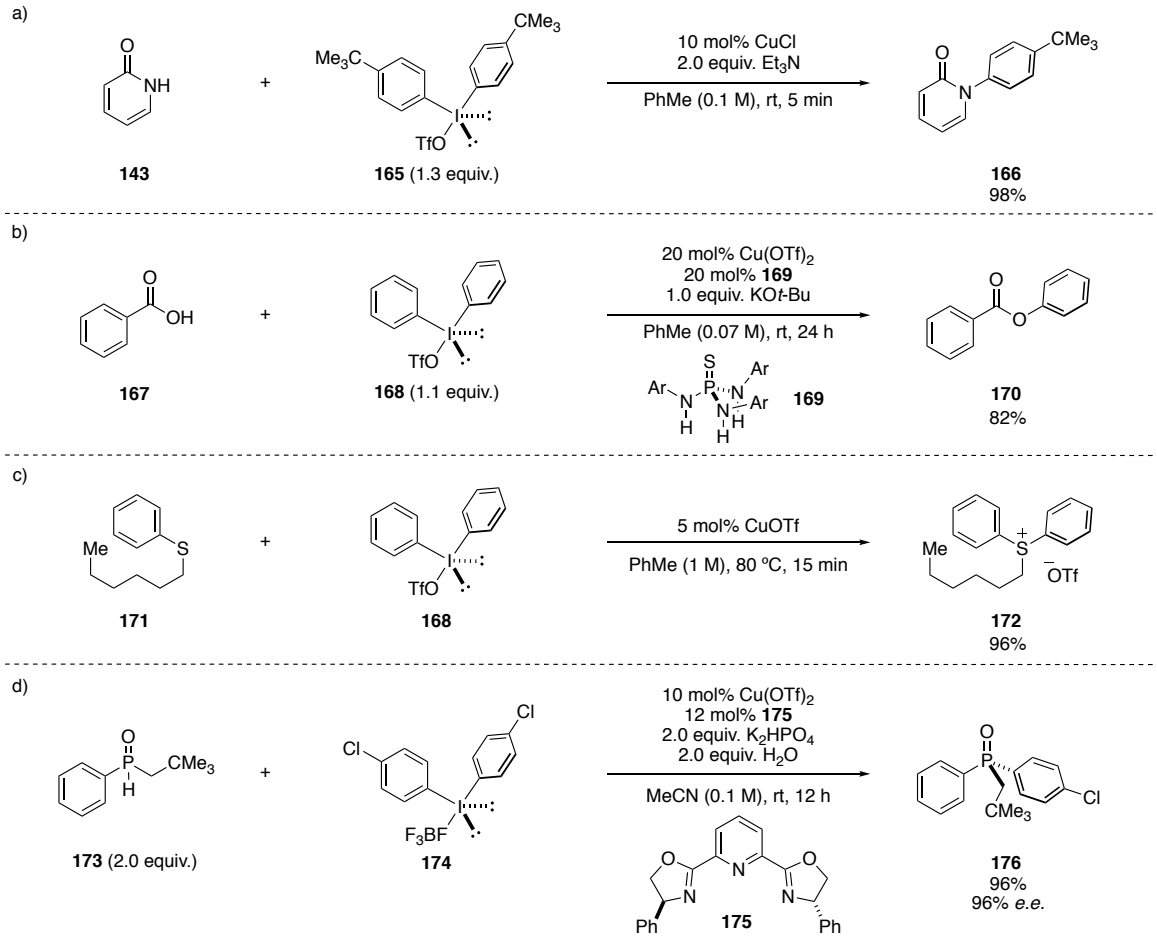


Figure 5 – Canty and Sanford's further investigations into the oxidative addition of copper (I) species with diaryliodonium salts; transition state energies are given as ΔG relative to the starting system in kcal mol-1 [101]

In analogy with palladium-catalysed methodologies, the combination of copper salts and iodonium salts has been employed to couple a wide variety of heteroatomic nucleophiles to aryl and alkenyl groups. Four examples of this reactivity are shown below (Scheme 30). Kim has demonstrated pyridiones to react very rapidly with diaryliodonium salts in the presence of copper(I) chloride (Scheme 30a).[103]

Nagorny has developed a dual copper and hydrogen-bond donor catalyst mixture to form phenolic esters from simple carboxylic acids and iodonium salts (Scheme 30b).[104] Krief has developed methodology for the copper-catalysed generation of sulfonium salts from thioethers and iodonium salts (Scheme 30c).[105] Finally, Gaunt has employed the chiral PyBOX ligand **175** to effect the arylative kinetic resolution of secondary phosphine oxides using copper-catalysis with symmetrical iodonium tetrafluoroborates (Scheme 30d).[106]



Scheme 30 –a) Kim's copper-catalysed pyridone arylation;[103] b) Nagorny's carboxylic acid arylation employing a synergistic copper hydrogen-bond door catalysis;[104] c) Krief's copper-catalysed thioether arylation giving sulfonium salts;[105] d) Gaunt's enantioselective secondary phosphine oxide arylation procedure[106]

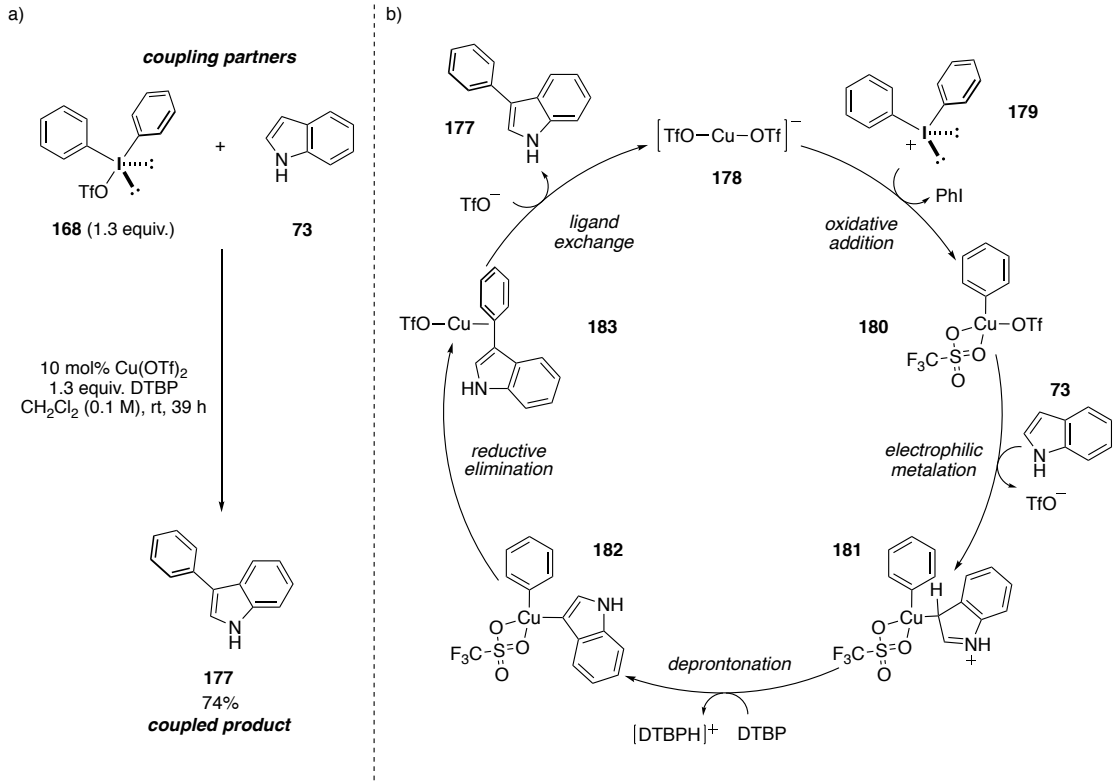
1.5 The Reactivity of Aryl and Alkenyl-Copper(III) Intermediates with Carbon Nucleophiles

With the high electrophilicity of the putative aryl- and alkenyl-copper(III) intermediates generated on the combination of iodonium salts and copper, much attention has been directed towards the use of this reaction manifold for carbofunctionalisation. In contrast with the limited reactivity of comparable palladium(II) species, it was hypothesised that the greater charge density of the copper(III) centre will allow for increased activity under milder conditions (*c.f.* section 1.2). The reaction of carbon nucleophiles

with high-valent copper(III) species was first tested with indole functionalisation under a Friedel-Crafts manifold.

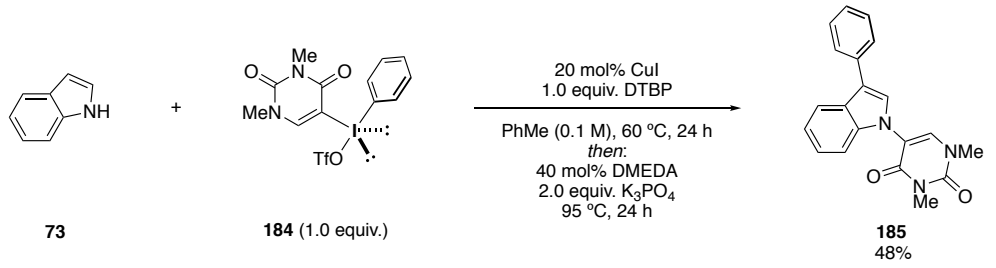
1.5.1. Friedel-Crafts interception of Cu(III) electrophiles

In line with Barton's elegant work employing organobismuth reagents,[107] Gaunt was able to generate C-3 arylated indoles using a combination of copper(II) triflate and diaryliodonium triflates (Scheme 31a).[108] In contrast to the majority of previous reports, this procedure gave C-3 arylated product rather than the C-2 substituted adduct, evidencing the reaction to occur through the expected electrophilic metalation pathway. To rationalise the observed reactivity, elements of Gaunt's proposed mechanism can be combined with insight gained from Sanford's work to form the following hybrid mechanism (Scheme 31b). In line with Sanford's studies, the active catalytic species is proposed to be copper(I) anion **178** and the cycle is proposed to begin on the association and oxidative addition of iodonium cation **179** to the starting copper(I) adduct. From here, the resulting κ^2-triflate-stabilised aryl-copper(III) intermediate **180** acts as a Friedel-Crafts electrophile, functionalising indole **73** at the C-3 position to give the cationic indole-copper(III) complex **181**. The electron-deficient nature of the copper centre precludes C-3 to C-2 migration, with simple deprotonation preferred to furnish the neutral copper(III) species **182**. A facile reductive elimination generates the C-3 arylated indole product **177**.



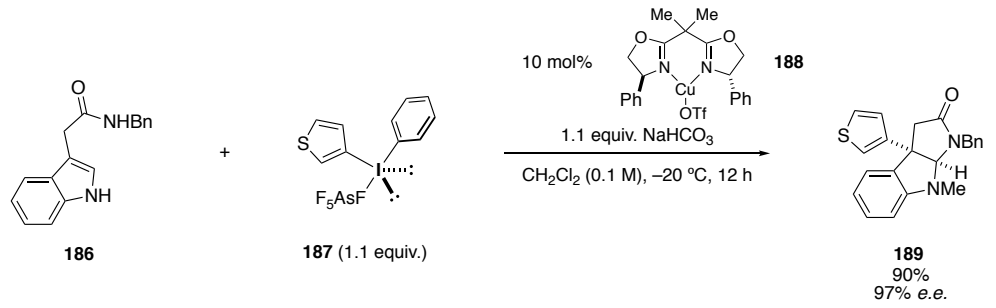
Scheme 31 – Gaunt's copper-catalysed C-3 indole arylation a) procedure[108] and b) proposed hybrid mechanism

This indole functionalisation process was exploited as the first step in Gaunt's 2015 synthesis of dictyodendrin B. Starting from cheap and commercial 4-bromoindole, arylation could be carried-out on a 42 g scale to furnish the 3-subsituted anisole adduct in 68% yield. The product was converted to the desired indolic natural product in twelve further steps.[109] Furthermore, You demonstrated the efficacy of the combination of copper and iodonium salts in the C-2 arylation and vinylation of 3-substituted indoles.[110] As an extension, Greaney has also shown that Gaunt's method can be combined with Ullmann-type chemistry to give double indole arylation in a one-pot procedure by consuming both aryl groups from the diaryliodonium salt (Scheme 32).[111]



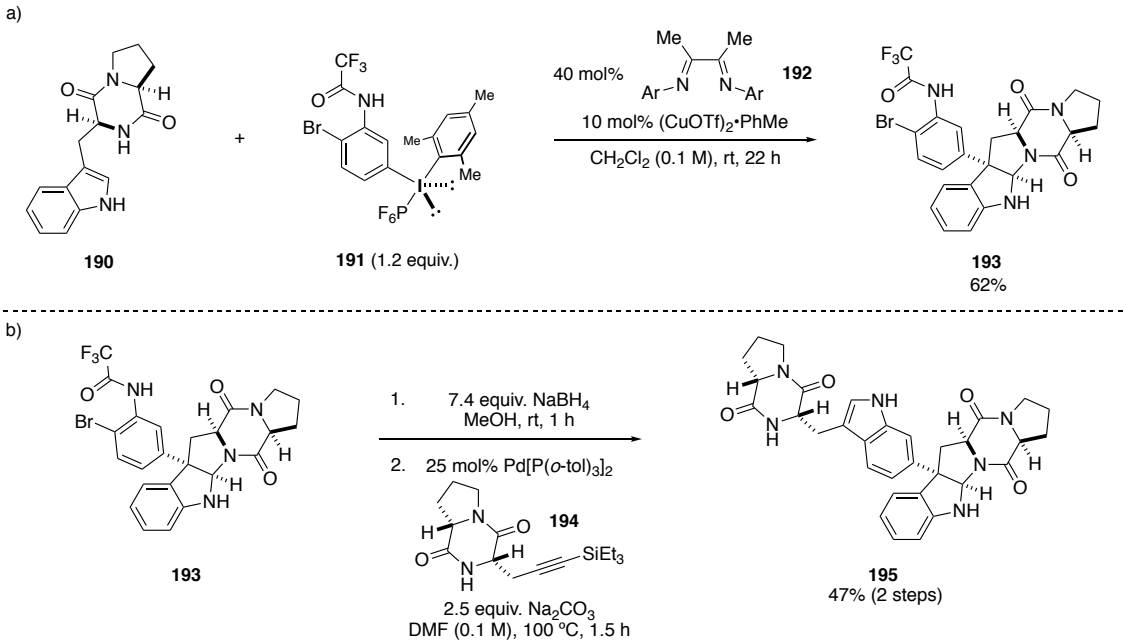
Scheme 32 – Greaney's double indole arylation[111]

The MacMillan, Reisman and You groups noted that the copper-catalysed reaction of iodonium salts with indoles bearing a C-3 pendant nucleophilic groups would allow the synthesis of pyrroloindolines by intramolecular trapping of the C-2 localised carbocationic intermediate.[112–115] MacMillan implemented this strategy by employing a chiral ligand backbone to give enantioenriched products (Scheme 33).



Scheme 33 – MacMillan's enantioselective pyrroloindoline synthesis employing copper catalysis and diaryliodonium salts[112]

Reisman's group was able to employ one of their methods in expedient syntheses of naseseazines A and B.[115] The synthetic strategy involved the transfer of brominated anilide iodonium salt **191** to the pendant indole of proline/tryptophan dimer **190**. C-2 cation trapping with the tryptophan amide yielded arylated polycycle **193** in 62% yield (Scheme 34a). Anilide **193** was then methonolysed and the product exposed to alkyne **194** in the presence of a palladium(0) source to undergo a Larock indolisation to give the desired pyrolloindoline product in 47% yield over two steps (Scheme 35b).[116]



Scheme 35 –Reisman's synthesis of naseseazine B **195** by a) copper-catalysed pyrroloindoline generation with diaryliodonium salt **191** and b) a palladium-catalysed indole formation with alkyne **194**[115]

In addition to indole functionalisation, Glorius has demonstrated that other electron-rich heterocycles undergo copper-catalysed Friedel-Crafts reactivity with iodonium salts.[117] Observed products include arylated furan, thiofuran and benzofuran species. Similarly, both Kumar and Wang have demonstrated that other nitrogenated heterocycles will react with iodonium salts in the presence of copper *via* an intermediate metalated species.[118,119] Kumar's approach employs lithiation whilst Wang's method proceeds through organozinc adducts. To date, nine further heterocycles have been functionalised using the copper/iodonium salt manifold (Table 3).

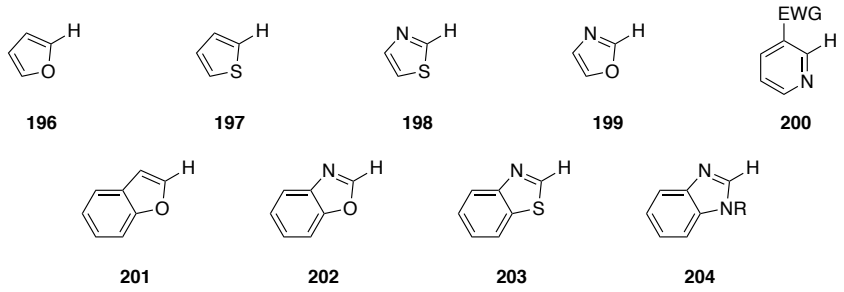
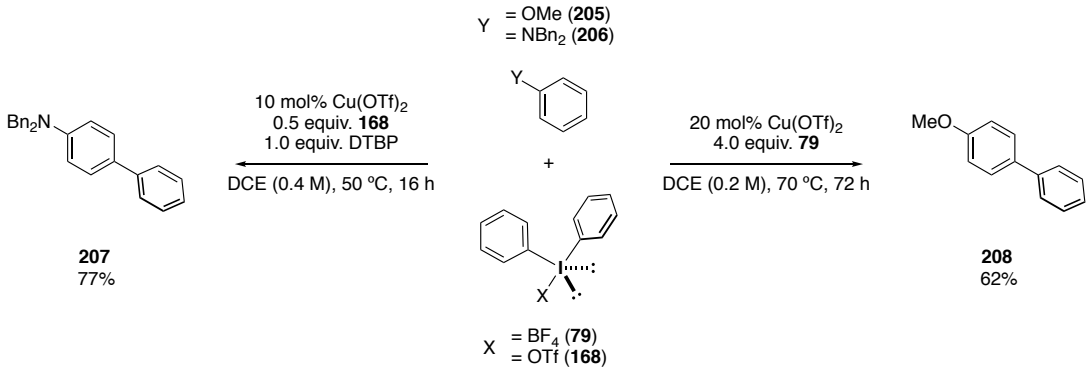


Table 3 – Heterocycles described to be functionalised using copper and iodonium salts with and without intermediate metalation[117–119]

The Gaunt group next turned their attention towards the application of the copper and iodonium salt reagent combination to anilines and anisoles, allowing selective functionalisation at the *para*-position of the substrates (Scheme 36).[120] The high *para*-selectivity observed contrasts with the majority of other metal-catalysed methods for the functionalisation of electron-rich benzene rings, generally observed to

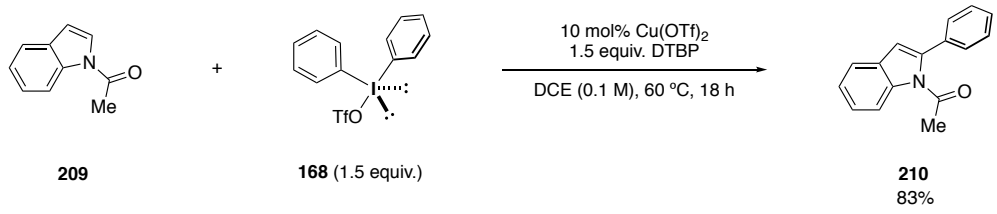
provide mixtures of *ortho-*/*meta-*/*para*-substituted products.[56,121–123] The highly selective reactivity observed under copper-catalysis provides further evidence that the reaction proceeds through electrophilic metalation rather than alternative C–H functionalisation mechanisms. Friedel-Crafts functionalisation of non-heteroaromatic arenes has been further extended by Hu and Wang to generate a broad suit of biphenyl species and to describe a general method for the *ortho*-arylation of *para*-substituted phenols.[124,125]



Scheme 36 – Gaunt's *para*-functionalisation of aniline and anisole substrates[120]

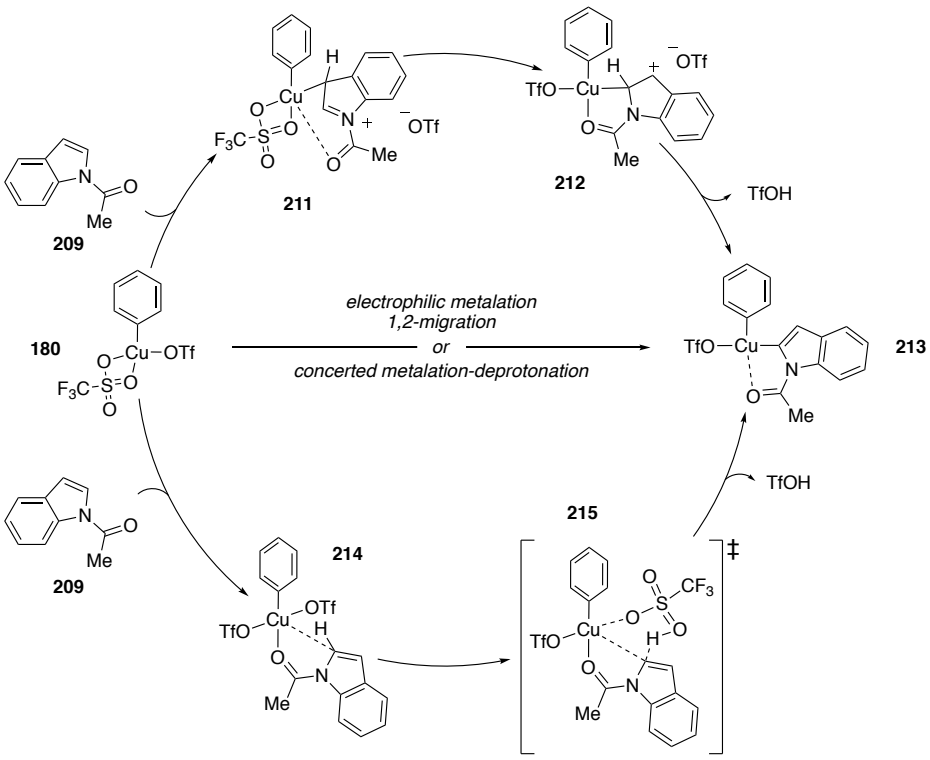
1.5.2. Non-classical aromatic functionalisation with Cu(III) electrophiles

During the course of studies into indole arylation with copper and iodonium salts, Gaunt noted that the natural C-3 selectivity of the reaction could be overturned with the use of *N*-acetylated indole **209** (Scheme 37).[108]



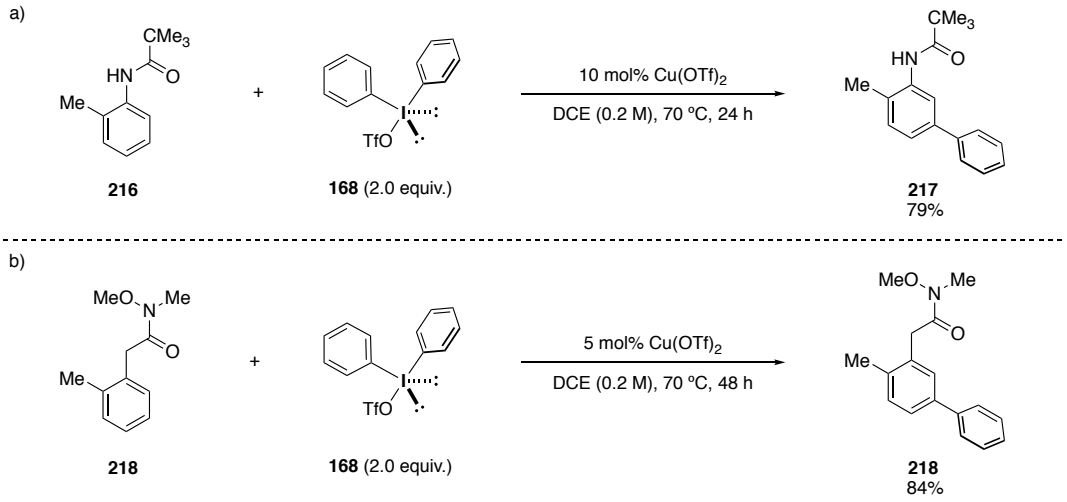
Scheme 37 – Gaunt's C-2 selective *N*-acyl indole arylation[108]

The switch in regioselectivity is attributable to the steering ability of the pendant carbonyl moiety, mechanistically explainable in two ways. Firstly, it is possible that the indole reacts through the C-3 position to generate Cu(III) adduct **211**, in line with the observation of C-3 arylation in the absence of a coordinating group (Scheme 31). The carbonyl group of the acetylated indole can then induce a C-3 to C-2 migration giving **213** *via* intermediate **212** (Scheme 38 – upper cycle). Reductive elimination would furnish the desired C-2 substituted product. Alternatively, the carbonyl group could directly bind aryl-copper(III) intermediate **214**. A concerted metalation-deprotonation process at the C-2 position would then directly generate catalytic intermediate **213** through a transition state such as **215** (Scheme 38 – lower cycle).



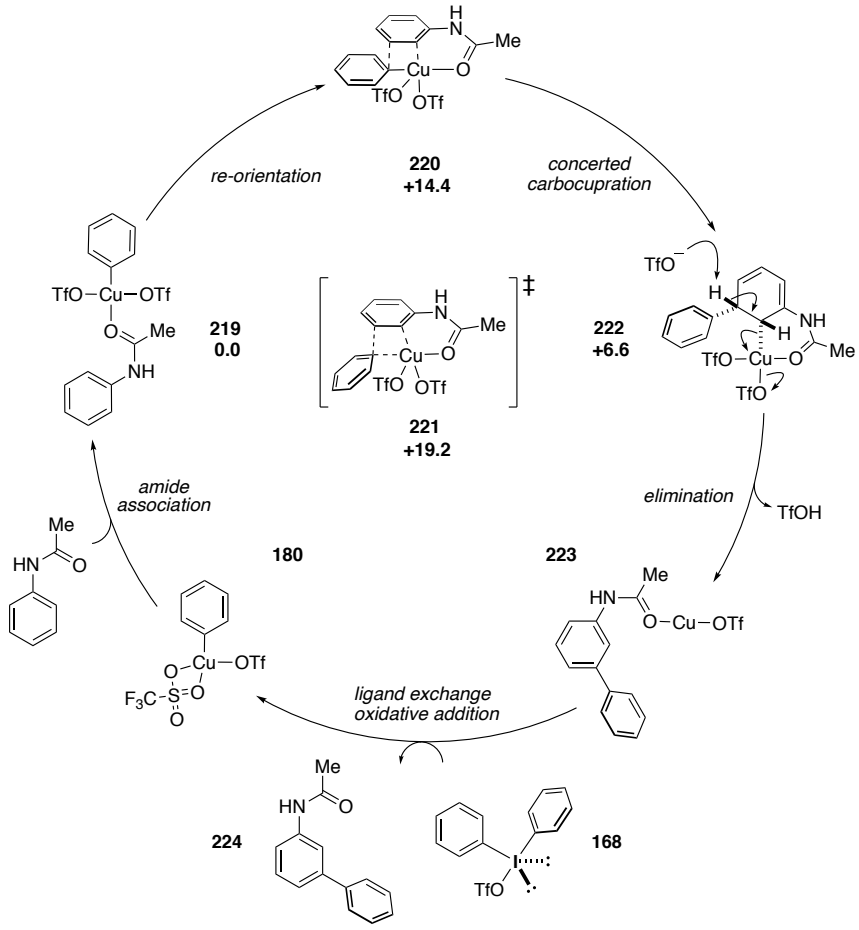
Scheme 38 – Proposed mechanistic origins of the Gaunt's C-2 selective N-acyl indole arylation procedure

Gaunt questioned whether the directing ability of carbonyl groups would allow for the non-natural functionalisation of other arene rings. Pursuing this strategy, he published in 2009 a highly *meta*-selective copper-catalysed pivanilide arylation (Scheme 39a).[126] The observed behaviour is in direct contrast with Daugulis' analogous palladium-catalysed *ortho*-arylation using the exact same substrate.[127] Interestingly, the *anti*-Friedel-Crafts reactivity could be reproduced on the copper-catalysed arylation of other α-aryl carbonyl species such as **218**, a structural analogue of pivanilide **216** (Scheme 39b).[128]



Scheme 39 –Gaunt's *meta*-selective arylation of a) pivanilides[126] and b) other α-aryl carbonyl species[128]

The origins of the non-natural selectivity of Gaunt's pivanilide arylation were computationally investigated by the Wu and Ding groups,[129,130] both evaluating the mechanism of the reaction using a simplified acetylanilide substrate (Scheme 40). It is computed that the ground-state Cu(III)-amide intermediate **219** initially re-orientates with an energetic penalty of +14.4 kcal mol^{-1} to give the apical aryl-associated copper(III) adduct **220**. This intermediate then undergoes a concerted carbocupration process, simultaneously *ortho*-cuprating and *meta*-arylating the anilide to give intermediate **222**. The transition state **221** for the *meta*-arylation process is calculated to lie at an accessible +19.2 kcal mol^{-1} above adduct **219**. Elimination, releasing an equivalent of triflic acid, re-aromatises the anilide ring and furnishes the coupled-product-bound copper(I) species **223**. Product dissociation and re-oxidation gives resting copper(III) intermediate **180** ready for amide association to regenerate the starting complex.

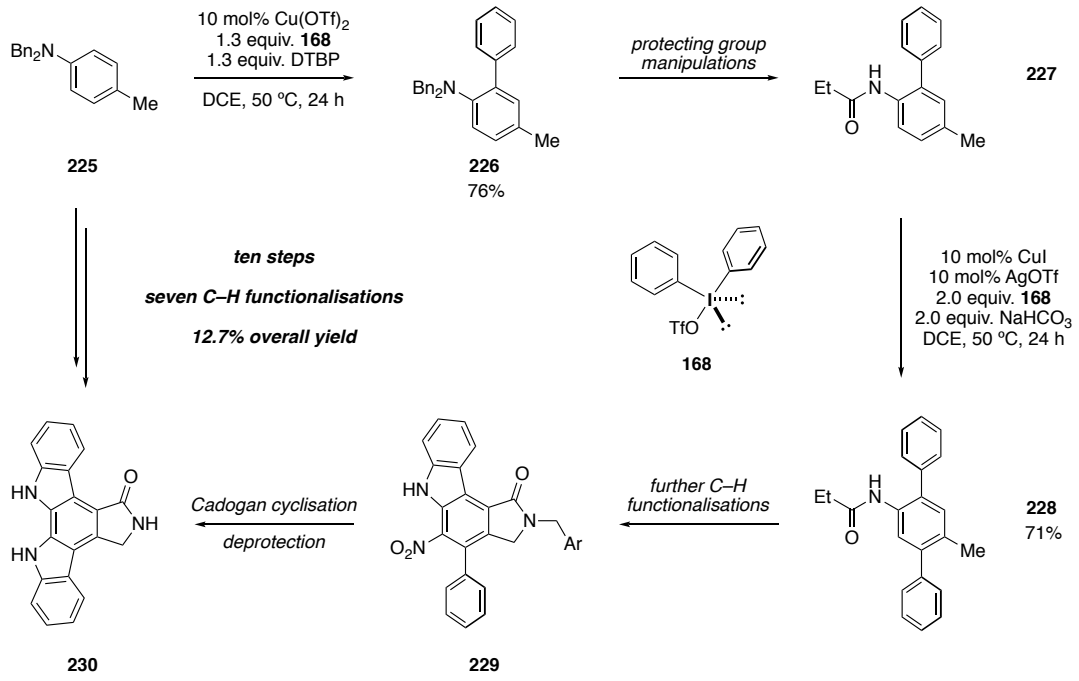


Scheme 40 – Wu's computational evaluation of Gaunt's copper-catalysed *meta*-selective anilide arylation;[129] bold quantities denote the relative energy of the system at that stage of the mechanism (kcal mol^{-1})

The Wu and Ding groups have also calculated the energetic barrier to the formation of the Friedel-Crafts-favoured *ortho*-arylated product. Both studies predict that the *ortho*-functionalisation would occur through a concerted metalation-deprotonation pathway with triflate acting as the base. Wu calculated an intermolecular carbonyl-directed CMD process whilst Ding computed an amide N–H directed bond formation/cleavage process. In both instances the energies of the transition states are calculated to be

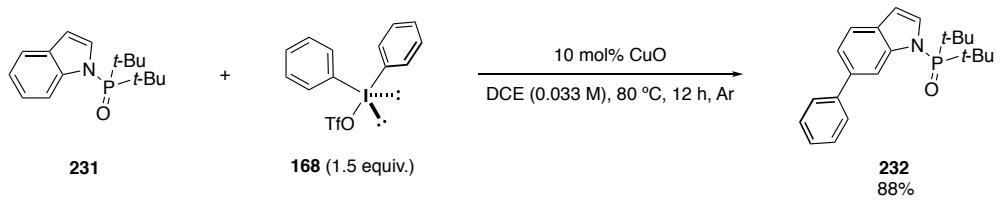
higher in energy than those leading to *meta*-functionalisation ($\Delta G^{\ddagger}$ = +2–7 kcal mol^{-1}). Interestingly, the relative energetic similarity of the *ortho*- and *meta*-arylation transitions states imply the accessibility of two potential processes for the functionalisation of arenes (carbocupration *vs.* CMD) under the investigated copper/iodonium salt manifold. The computed accessibility of a CMD process with a pivanilide substrate supports the second mechanistic proposal for the C-2 indole arylation described above (Scheme 38, lower cycle).

Gaunt's modular synthesis of the indolocarbazole natural product staurosporinone **230** employs both *meta*- and *ortho*-selective copper-catalysed arylation procedures. These reactions are employed to introduce pendant phenyl groups to an aniline core, later constructed *via* five further C–H functionalisation processes into the desired product (Scheme 41).[131] This strategy allowed the synthesis of staurosporinone in ten steps and in 12.7% overall yield. It was envisaged that the use of derivatised iodonium salts in the synthetic route would allow for the generation of a range of unsymmetrical staurosporinone analogues.



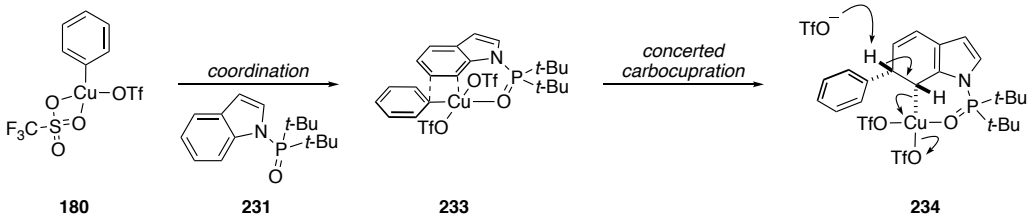
Scheme 41 – Gaunt's total synthesis of staurosporinone **230** employing two copper-catalysed arylations[131]

Shi has further elaborated the concept of directing functionalisation to non-natural ring positions. His group has described a C-6 selective indole arylation/alkenylation procedure using copper and iodonium salts. Inspired by previous palladium-catalysed studies giving C-7-selective indole functionalisation,[132] the reaction uses a phosphinic amide to direct reactivity towards the desired position (Scheme 42).[133]



Scheme 42 – Shi's C-6 selective indole arylation intramolecularly directed by a phosphinic amide moiety[133]

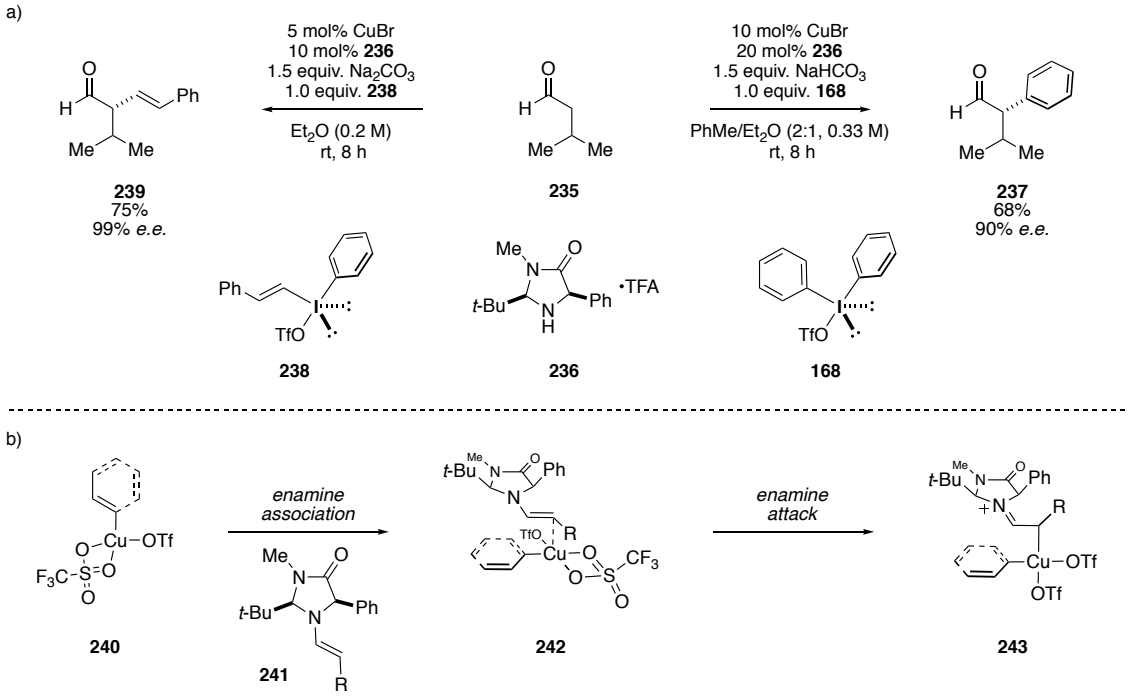
It is proposed that the steric bulk of the *tert*-butyl groups of phosphinic amide **231** helps orientate the directing group towards the six-membered ring portion of the indole. From here, the mechanistic proposal is analogous to that described by Wu and Ding in their computational investigations into the *meta*-selective anilide arylation. Co-ordination of the phosphoryl moiety to the aryl-copper(III) intermediate **180** places the electrophilic metal centre under the indolic C-7 position and the aryl group under C-6. A concerted carbocupration process provides the desired carbon-carbon connectivity, generating formal alkyl copper intermediate **234**. Elimination of this species would regenerate copper(I) and furnish the observed C-6 functionalised indole (Scheme 43).



Scheme 43 – Proposed mechanism for Shi's C-6 selective indole arylation

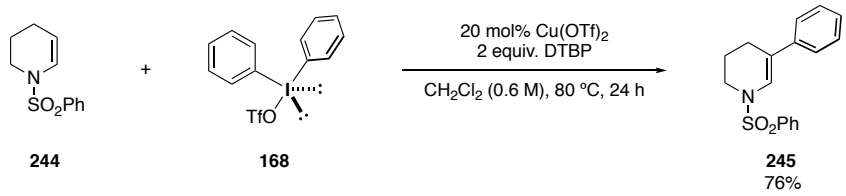
1.5.3. α-Carbonyl functionalisation with Cu(III) electrophiles

The earliest examples of non-aromatic carbofunctionalisation processes using copper and iodonium salts employed enolate equivalents as the nucleophilic coupling partners. The first report of this type was MacMillan's procedure for the enantioselective α-arylation of aldehydes using iodonium salts using a synergistic catalyst system of a copper salt and organocatalyst **236** (Scheme 44a).[134] The same process has also been performed with alkenyl(aryl)iodonium salts to give aldehyde α-vinylation.[135] It is proposed that the reaction proceeds through coordination of pre-formed enamine **241** to copper(III) intermediate **240**. The bound enamine then attacks the copper centre to give alkyl-copper species **243**. Reductive elimination and hydrolysis then provides the α-functionalised aldehyde (Scheme 44b).



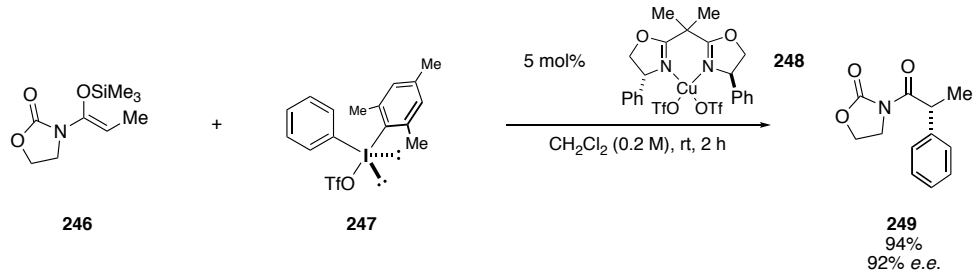
Scheme 44 – a) MacMillan's enantioselective aldehyde α-arylation and α-vinylation procedures;[134,135] b) proposed mechanism and origin of enantioselectivity

Applying similar reactivity to an achiral system, Pannecoucke, Gillaizeau and Kesavan have demonstrated that cyclic enamides may undergo copper-catalysed arylation and vinylation with iodonium salts to give a range of functionalised piperidines (Scheme 45).[136,137]



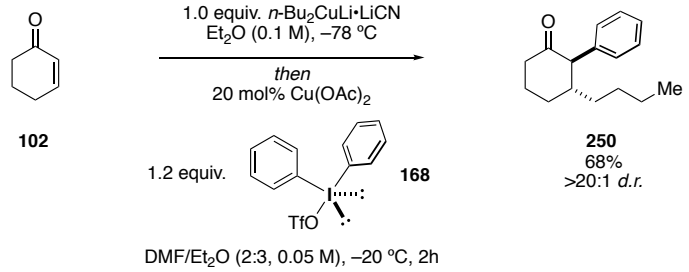
Scheme 45 – Pannecouke and Gillaizeau's enamide arylation[136]

Both the Gaunt and MacMillan groups further applied the concept of copper-catalysed asymmetric electrophilic arylation to the reaction of silyl ketinimides. Publishing in 2011, the groups described analogous reactions controlled by the presence of a chiral bisoxzoline ligand around the copper centre. MacMillan used a TBS-protected ketinimide, hexafluorophosphate iodonium salts and a copper(I) catalyst to effect the transformation, whilst Gaunt used a TMS-protected substrate, triflate iodonium salt and copper(II) complex **248** (Scheme 46).[138,139]



Scheme 46 – Gaunt's enantioselective silyl ketinimide arylation with copper-bisoxazoline complex **248**[138]

Finally, Zhang and co-workers have elaborated a one-pot conjugate addition and arylation reaction to functionalise enones at both α- and β- positions in high *anti*-diastereoselectivity. This procedure relies on the addition of Gilman reagent to a cyclic α,β-unsaturated ketone before trapping the resulting enolate with an iodonium salt in the presence of further catalytic quantities of copper (Scheme 47).[140]

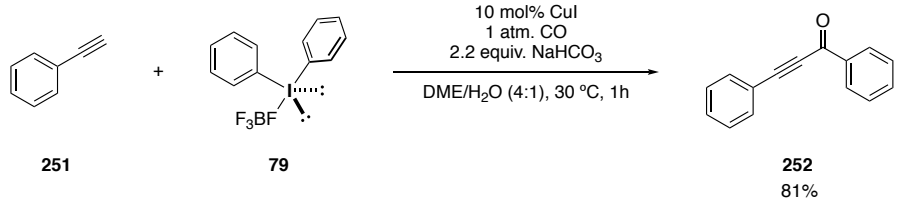


Scheme 47 – Zhang's generation of α-aryl, β-alkyl ketones from simple enones[140]

1.5.4. Alkyne functionalisation with Cu(III) electrophiles

1.5.4.1 Terminal alkyne functionalisation

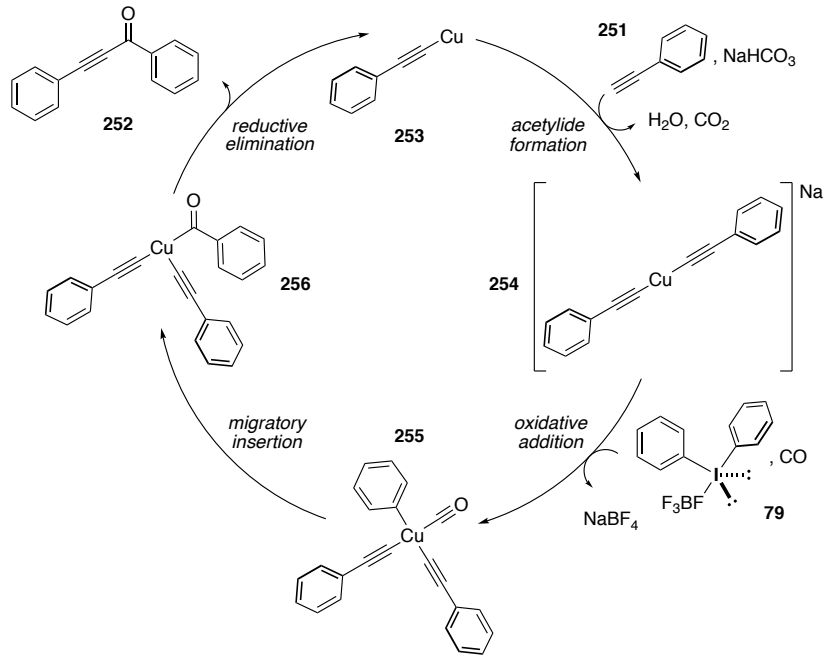
The functionalisation of terminal alkynes with copper(I) species and iodonium salts was first described in Kang's 1997 investigations into carbonylative Sonogoshira-type processes. Despite investigations initially focusing on the use of both palladium and copper, the reaction of alkyne **251** with diphenyliodonium tetrafluoroborate was observed to proceed with only the addition of copper as a catalyst (Scheme 48).[141]



Scheme 48 – Kang's copper-catalysed carbonylative Sonogoshira reaction with iodonium salts[141]

The reaction mechanism can be proposed to begin with the formation of bisalkynylated copper(I) anion **254** from copper(I) acetylide **253**. This anionic species may undergo oxidative insertion with the

iodonium salt to give adduct **255** following carbon monoxide association. 1,1-Migratory insertion of the CO ligand into the Cu–aryl bond would provide acyl-bound copper(III) species **256**. Reductive elimination would occur from this intermediate to furnish the product and re-generate copper(I) acetylide (Scheme 49).

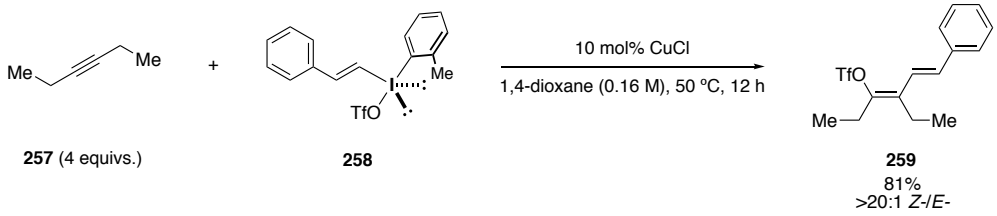


Scheme 49 – Proposed mechanism for Kang's carbonylative Sonogoshira-type reaction

Though Kang's work has been more recently extended to a classical Sonogoshira process,[142] there have been few further developments using solely copper as a catalyst for this coupling mode. The majority of systems for terminal alkyne coupling favour a mixed palladium/copper catalyst system.[143]

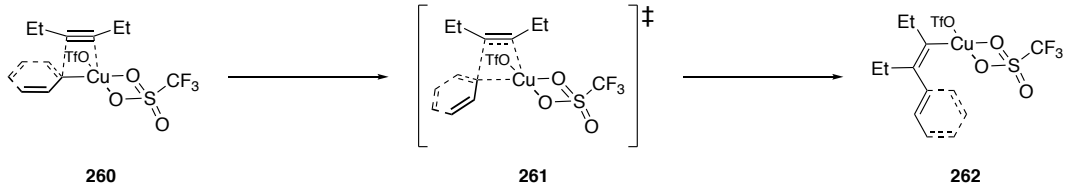
1.5.4.2 Internal alkyne functionalisation

Interested in the functionalisation of less intrinsically-nucleophilic carbon-based functional groups, the Gaunt group turned their attention towards the derivitisation of internal alkynes using copper catalysis and iodonium salts. Such a process was first described with the generation of vinyl triflates *via* a *syn*-carbotriflation process, demonstrated to be particularly successful for the generation of dienyl triflates from alkynes and alkenyl iodonium salts (Scheme 50).[144]



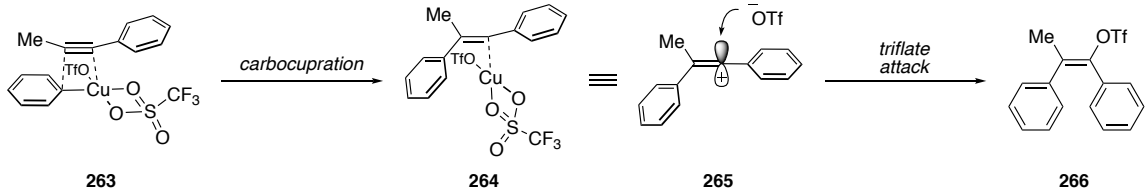
Scheme 50 – Gaunt's *Z*-selective alkyne carbotriflation with alkenyl iodonium salts under copper catalysis[144]

The formation of the vinyl triflate product is proposed to occur through adduct **260**, formed by the initial coordination of an alkyne to an *in situ* generated copper(III) species. The high *Z*-selectivity of the product indicates the functionalisation mechanism to proceed through a concerted carbocupration mechanism, giving alkenyl-copper(III) species **262** *via* a transition structure such as **261** (Scheme 51). Reductive elimination will furnish the triflate-coupled product.



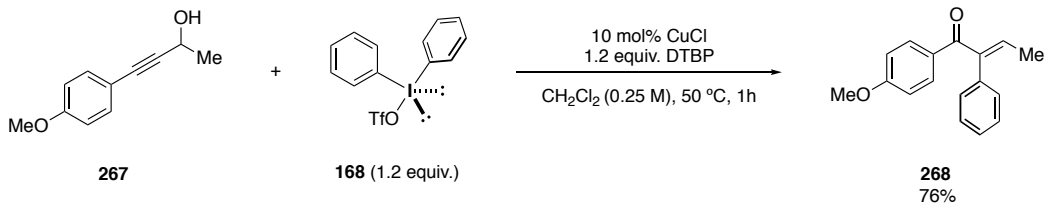
Scheme 51 – Concerted carbocupration mechanism towards *syn*-functionalisation of alkynes

It was observed during Gaunt's studies that the use of phenyl-substituted unsymmetrical alkynes led to the formation of the *E*-configured vinyl triflate. The reversal in stereoselectivity can be attributed to the formation of either a vinyl cation (**265**) or some vinyl-cation-like copper(III) intermediate (**264**). The highly electrophilic intermediate would be attacked by a free triflate ion approaching from the least sterically constrained trajectory to give the observed alkenyl triflate geometry (Scheme 52).



Scheme 52 – Proposed *E*-selective vinyl triflate formation *via* a vinyl-cation like species

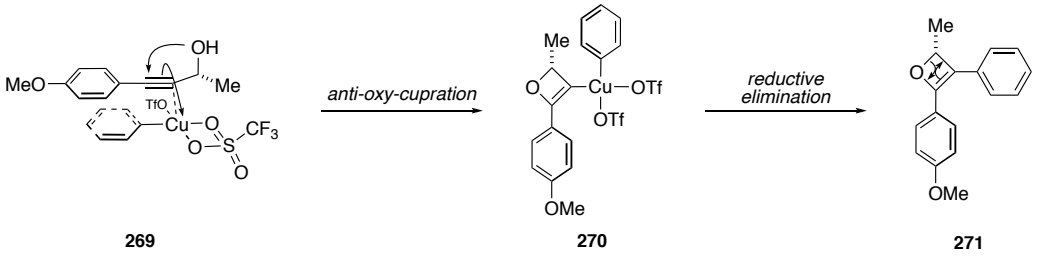
The Liu and Gaunt groups both noted unsymmetrical propargylic alcohols to re-arrange on exposure to iodonium salts in the presence of a copper catalyst to furnish α,β-unsaturated ketones. This Meyer-Schuster-type reactivity[145] was exploited to generate 45 examples of α,β-unsaturated carbonyl compounds and their corresponding hydrates (Scheme 53).[146,147]



Scheme 53 – Gaunt's copper-catalysed arylative Meyer-Schuster reaction[146]

The Liu group proposed the observed reactivity to result from a 4-*endo*-dig *anti-oxy*-cupration from alkyne co-ordinated Cu(III) intermediate **269**. Reductive elimination of the resulting product would generate oxetene intermediate **271** which would rapidly undergo an electrocyclic ring opening to yield the desired

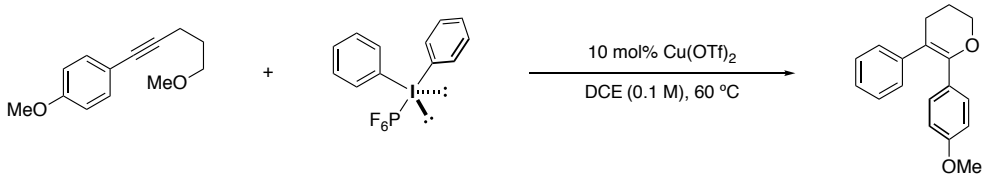
unsaturated ketone (Scheme 54).[147] However, it should be noted that the same oxetene intermediate could be generated *via* the intermediacy of a vinyl-cation or some equivalent copper(III)-bound intermediate (*c.f.* Scheme 52 above, intermediates **264** and **265**). In the place of the above triflate addition, *anti*-attack with the pendant alcohol would occur.



269 **270** **271**

Scheme 54 –Liu's mechanistic proposal involving an *anti-oxy*-cupration and an electrocyclic ring-opening[147]

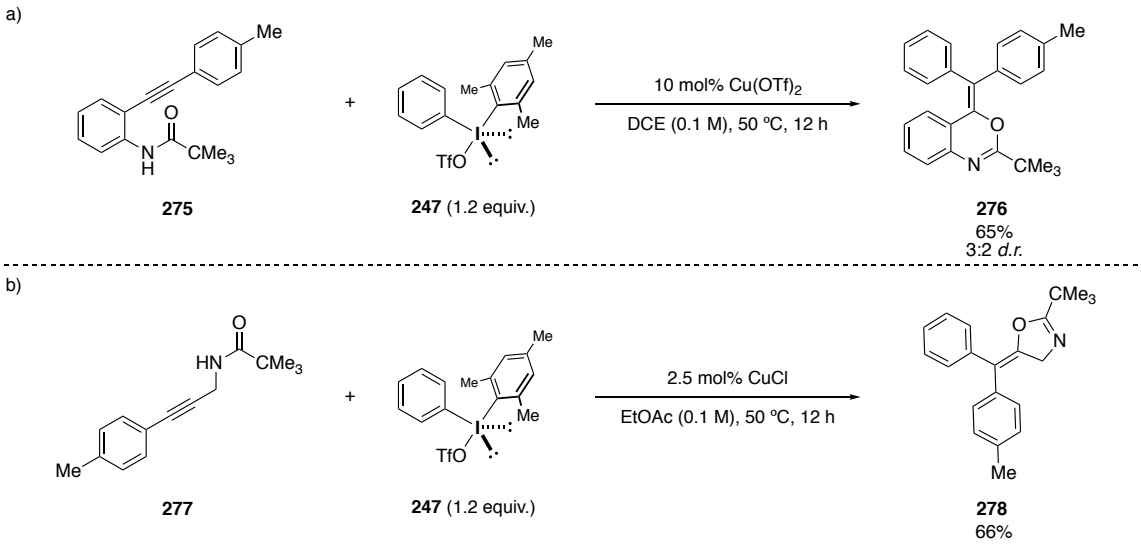
Qu reported another alkyne *anti-oxy*-arylation process giving the formation of dihydrofurans and dihydropyrans from unsymmetrical aryl/alkyl-alkynes bearing pendant ether groups (*e.g.* **272**).[148] These substrates were treated with an iodonium salt and a copper catalyst to generate a range of 5- and 6-membered cyclic vinyl ethers (Scheme 55).



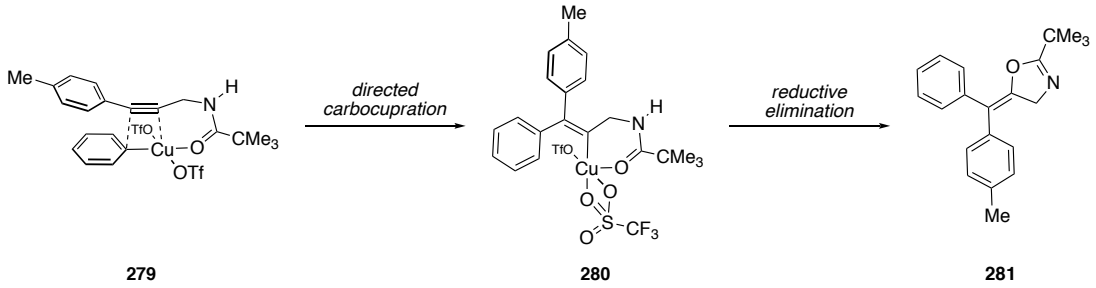
272 **273** (1.2 equiv.) **274** 62%

Scheme 55 – Qu's copper-catalysed generation of dihydrofurans and dihydropyrans[148]

Novák has also employed a tethered nucleophile strategy to generate both benzoxazines and oxazolines by the copper-catalysed arylation of two carefully-designed alkyne substrates using iodonium salts (Scheme 56).[149,150] Interestingly, the products of the two reactions are formed with *anti*- and *syn-oxy*-arylation respectively. Additionally, in contrast with previous examples, the formation of oxazoline **278** occurs with arylation at the less intrinsically-nucleophilic alkyne position, implying its formation through a carbonyl-directed carbocupration/reductive elimination process (Scheme 57).

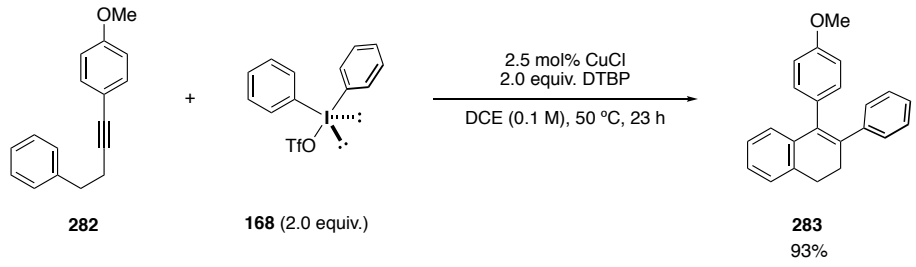


Scheme 56 – Novák's a) benzooxazine formation[149] and b) oxazoline formation[150]

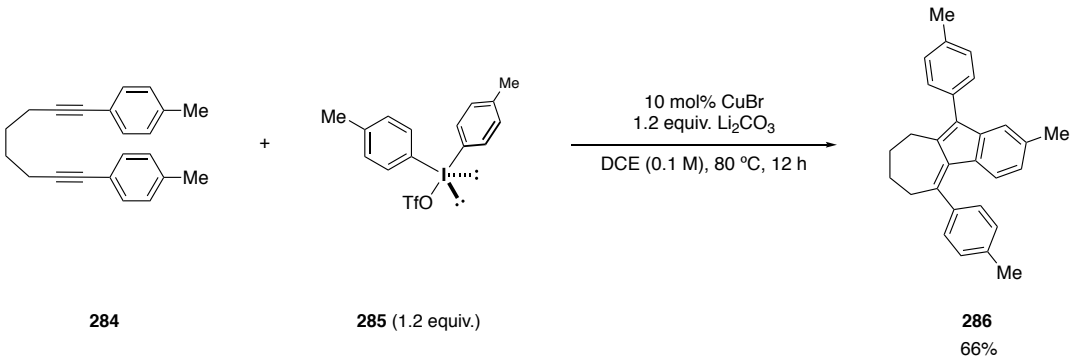


Scheme 57 – Proposed mechanistic origin of Novák's unnatural alkyne arylation furnishing oxazolines

The Gaunt group has demonstrated tethered arenes to act as nucleophiles in the carboarylation of alkynes (Scheme 58).[151] The *in situ*-generated reactive species is thought to be quenched in a Friedel-Crafts manner to generate a range of polycyclic hydrocarbons. Given the high electrophilicity required for such a process, the reaction is proposed to proceed *via* a vinyl-cation-like intermediate. The Chen group have used similar chemistry to successfully effect a carbocationic relay giving diyne bicylisation (Scheme 59).[152]



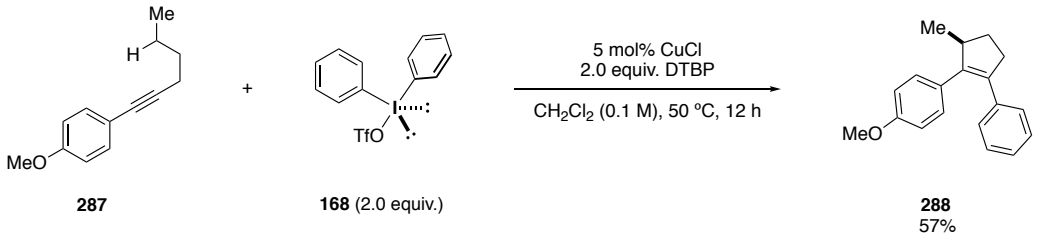
Scheme 58 – Gaunt's alkyne carboarylation to give polycyclic hydrocarbons[151]



284 **285** (1.2 equiv.) **286** 66%

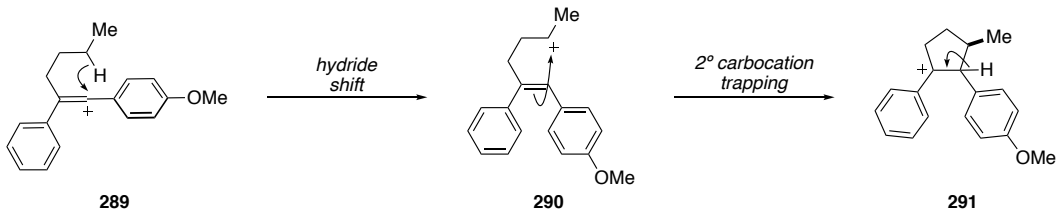
Scheme 59 – Chen's diyne bicyclisation *via* a carbocation relay[152]

Finally, the Gaunt and Chen groups have both published migratory cyclisation reactions, induced by a copper-catalysed alkyne arylation process, appearing to proceed through insertion into a C–H bond (Scheme 60).[153,154] Gaunt rationalised the observed reactivity through the occurrence of a 1,5-hydride to quench the putative vinyl-cation intermediate **289**, transferring the positive charge to a secondary alkyl centre (**290**). The electron-rich alkene would then trap this transient electrophilic centre to give benzylic carbocation **291**. Elimination from the most acidic proton would furnish the observed product (Scheme 61).



287 **168** (2.0 equiv.) **288** 57%

Scheme 60 – Gaunt's synthesis of pentenes *via* a C–H insertion/cyclisation strategy[153]

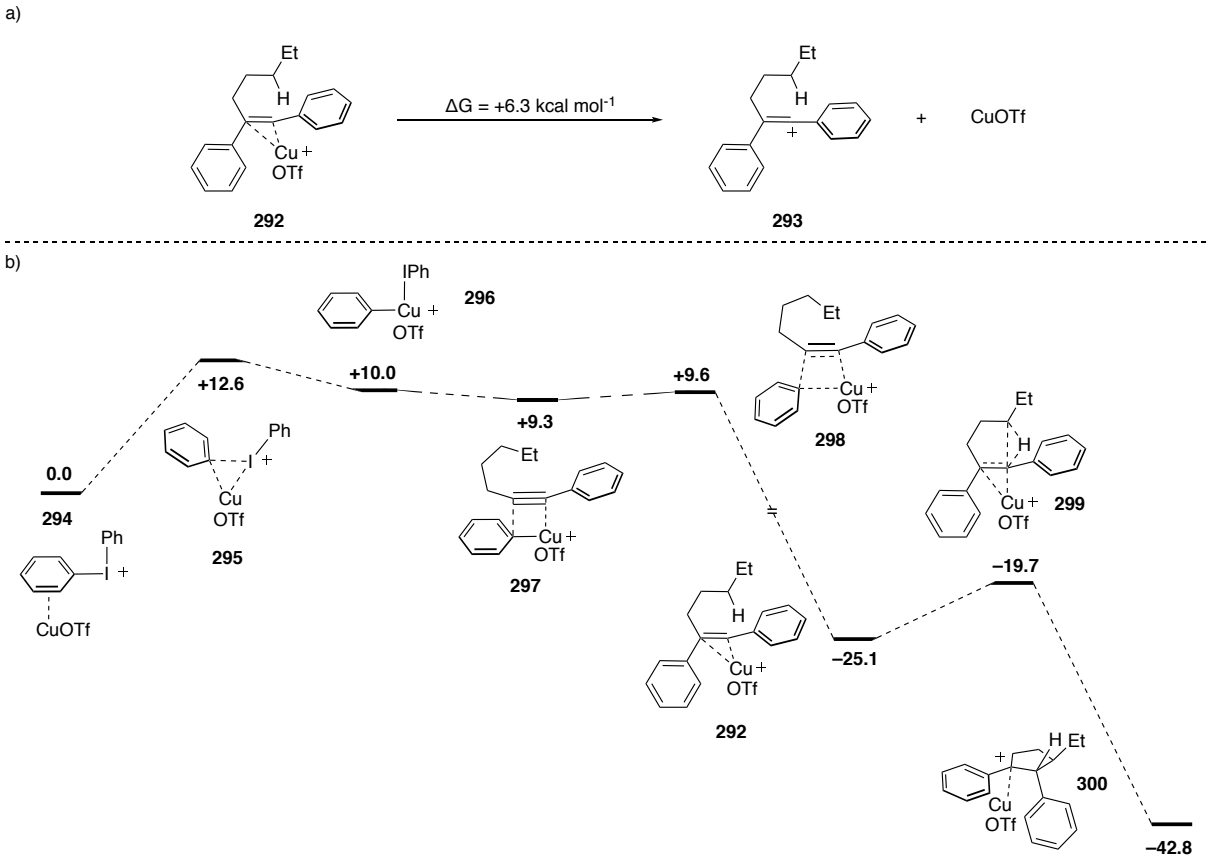


289 **290** **291**

Scheme 61 – Gaunt's proposed cyclisation mode to furnish pentene **288**

However, Chen's group computationally investigated the origins of the observed migration cascade and determined copper(III)-bound vinyl cation **292** to be lower in energy than the corresponding free vinyl cation **293** (Scheme 62a). Furthermore, no secondary carbocationic intermediate (as required for the stepwise mechanism above) could be computationally isolated. The computational evidence indicated the copper centre to be mechanistically important for the migration/cyclisation steps of the reaction. It was determined that the desired product could be accessed *via* a concerted migration and trapping

process with the participation of the copper catalyst. An energy profile for this process is shown below (Scheme 62b).[154]



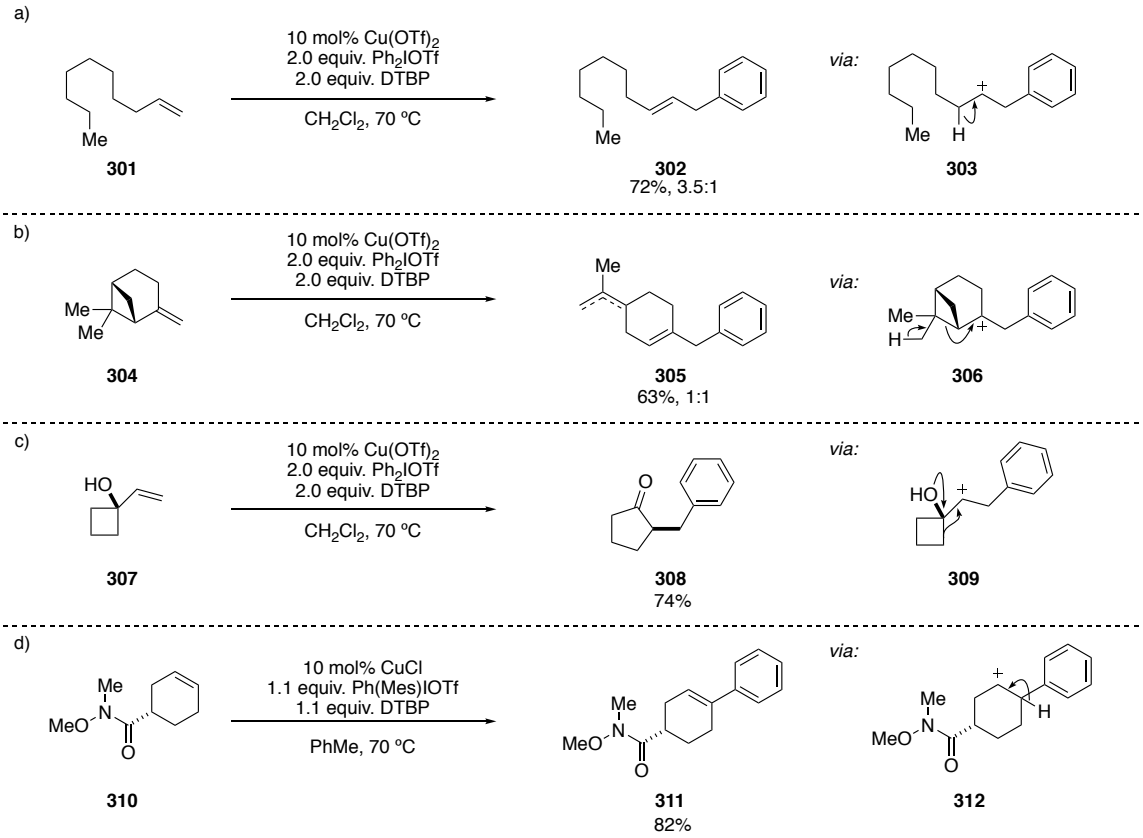
Scheme 62 – a) comparison of relative energies of copper(III) bound vinyl cation equivalent and free vinyl cation; b) energy profile for concerted C–H migration and secondary carbocation trapping (energies are given as ΔG relative to the starting system in kcal mol-1)[154]

The reaction is computed to proceed by association of the alkyne to phenyl-copper(III) intermediate **296**, generated by oxidative addition of copper(I) triflate into a diphenyliodonium cation. There is observed to be little energetic penalty to the carbocupration process giving vinyl-cation-like species **292** ($\Delta G^{\ddagger}$ = +0.3 kcal mol-1). A transition state (**299**) with characteristics of 1,5-hydride transfer and simultaneous alkene attack was determined to be accessible ($\Delta G^{\ddagger}$ = +5.4 kcal mol-1), allowing the generation of adduct **300** for simple elimination.

1.5.5. Alkene functionalisation with Cu(III) electrophiles

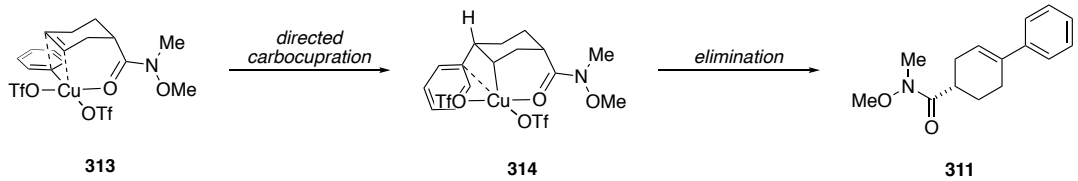
The copper-catalysed functionalisation of alkenes using iodonium salts was first described by the Gaunt group in 2012. Rather than providing products that would be expected for a Heck reaction mechanism, reactivity was observed to proceed with carbocation-like behaviour. A large number of reactions were performed to demonstrate the breadth of the reactivity.[155] Examples include simple alkene arylation to give non-conjugated alkene products (Scheme 63a) and classical β-pinene and semipinacol-type

rearrangements (Schemes 63b and c). Interestingly, the scope of this latter semipinacol rearrangement has recently been expanded and the transformation made enantioselective.[156]



Scheme 63 – Gaunt's alkene simple alkene functionalisation displaying carbocation-like behaviour;[155] a) simple alkene arylation to give a stepped alkene product; b) arylative fragmentation of β-pinene; c) arylative semi-pinacol rearrangement; d) carbonyl-directed alkene arylation

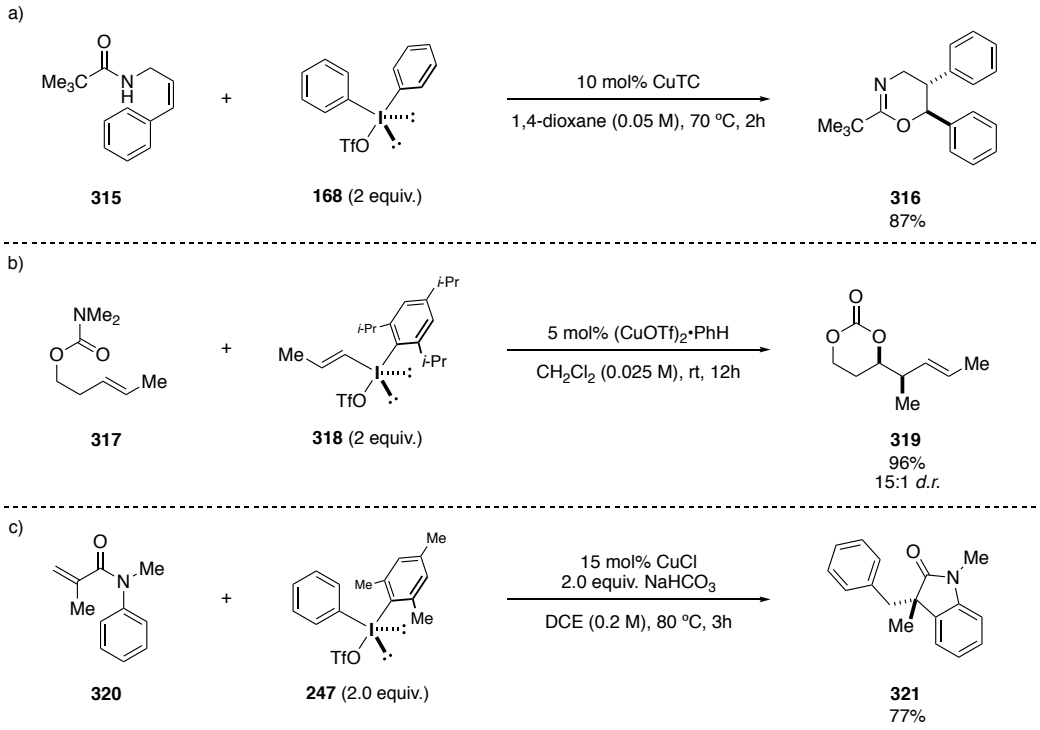
Distinctly, it was observed that carbonyl-bearing substrate **310** gave arylation to form only one product (Scheme 63d). This reactivity is attributable to the directing ability of the Weinreb amide (Scheme 64). Analogous to Chen's computation of a vinyl-cation-like copper(III) intermediate, the exclusive formation of product **311** could imply the existence of a formally copper-bound species (*e.g.* **314**) that behaves analogously to a carbocationic intermediate.



Scheme 64 – Proposed alkene functionalisation by directed carbocupration

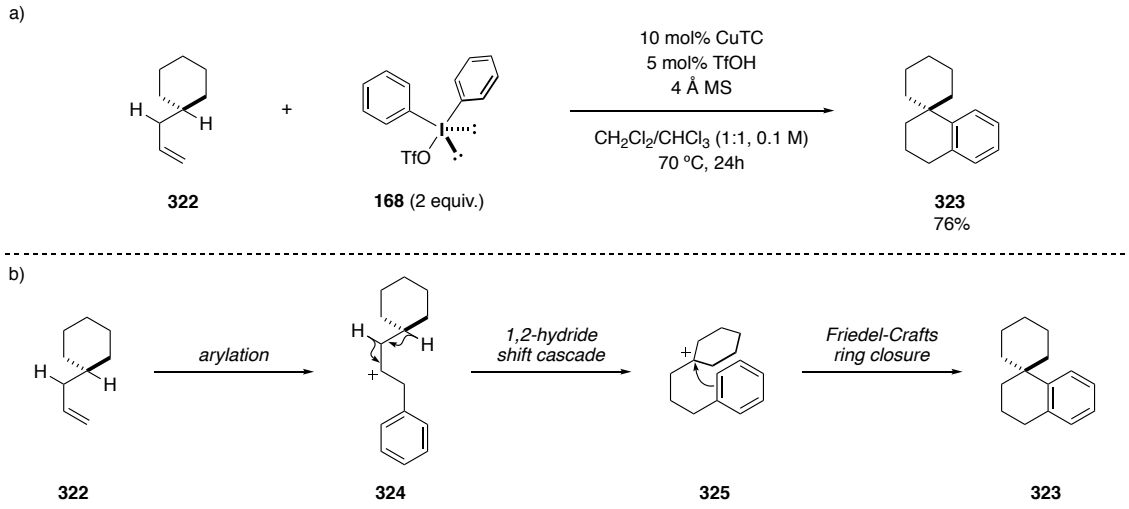
The Gaunt group has also developed copper-catalysed alkene functionalisation processes using iodonium salts where the *in situ* generated carbocation-like intermediate is intercepted by a pendant

nucleophile. This concept was exploited to diastereoselectivity transform allylic amides and homoallylic carbamates into oxazines and homoallylic carbonates respectively (Scheme 65a and b).[157,158] Similarly, Zhou, Li, Fun and Tang have employed Friedel-Crafts nucleophilicity to trap the carbocation-like intermediate formed on the treatment of *N*-aryl-acrylamides with copper and diaryliodonium salts (Scheme 65c).[159–161]



Scheme 65 – a) Gaunt's *oxy*-arylation strategy to generate oxazines;[157] b) Gaunt's *oxy*-alkenylation to generate homoallylic carbonates;[158] c) Zhou and Li's oxindole synthesis[159]

Lastly, Gaunt and co-workers have developed a cascade arylation procedure to generate a series of tetralins from the copper-catalysed functionalisation of terminal alkenes with iodonium salts (Scheme 66a). The reaction is proposed to proceed *via* the intermediacy of carbocation-like intermediate **324**, formed by the arylation of **322**. The electrophilic species then undergoes a 1,2-hydride shift cascade to give carbocation **325**. Finally, this intermediate undergoes an intramolecular Friedel-Crafts reaction with the aryl group to give the desired tetralin (Scheme 66b).



Scheme 66 – a) Gaunt's copper-catalysed tetralin synthesis;[153] b) simplified mechanistic scheme for this process

It can be seen from the above studies that a variety of alkenes can undergo functionalisation on treatment with copper and iodonium salts to provide a range of arylated and vinylated products, apparently formed through a variety of different mechanisms. Work is required to further extend and understand this observed reactivity.

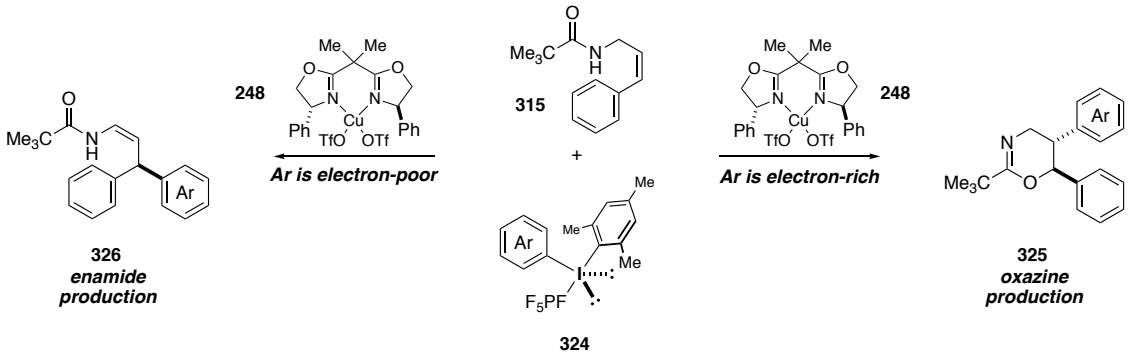
1.6 Summary

The combination of copper salts and iodonium salts has been demonstrated to be a rich strategy for the functionalisation of nucleophilic groups. Compelling evidence suggests the intermediacy of aryl- and alkenyl-copper(III) species in these systems, with the copper(III) intermediates appearing to react as potent sp^2-hybridised carbocation equivalents. Their highly electrophilic behaviour contrasts with analogous palladium(II) systems, allowing the development of reactions that proceed under mild conditions and by distinct functionalisation modes. Novel reactivity observed under this copper-catalysed manifold includes non-classical carbofunctionalisation, enantioselective arylation/vinylation and the induction of carbocation-like reactivity on alkynes and alkenes. The combination of copper and iodonium salts requires significant further understanding to maximise its potential in organic chemistry.

2 Enantioselective and Regiodivergent Copper-Catalysed Arylation of Allylic Amides with Diaryliodonium Salts

2.1 Project Overview

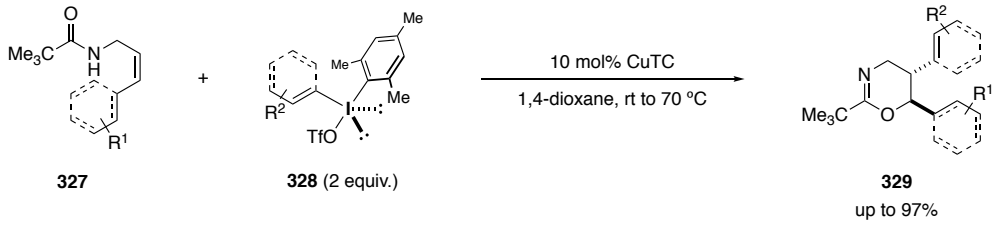
This chapter describes the development of a novel copper-catalysed enantioselective alkene functionalisation strategy. Initial efforts focused on the reaction of allylic amide substrates with diaryliodonium salts to furnish diarylated enamides in high *e.e.*. Working from an initial result, optimisation studies were carried out on the enamide formation process. No significant improvements in yield or *e.e.* were observed throughout these investigations. However, investigating the scope of the enamide formation reaction revealed that the regioselectivity of the alkene arylation process was sensitive to the electronic nature of the iodonium salt. It was observed that electron-poor diaryliodonium salts would react with allylic amides to give enamide products whilst the use of electron-rich diaryliodonium salts would furnish oxazines (Scheme 67). A scope of twenty enamides and eighteen oxazines was elaborated, giving product formation in synthetically useful yields and in universally high *e.e.*.



Scheme 67 – Overview of the electronically-controlled regiodivergent arylation of allylic amide **315** with diaryliodonium salt **324**

2.2 Project Background

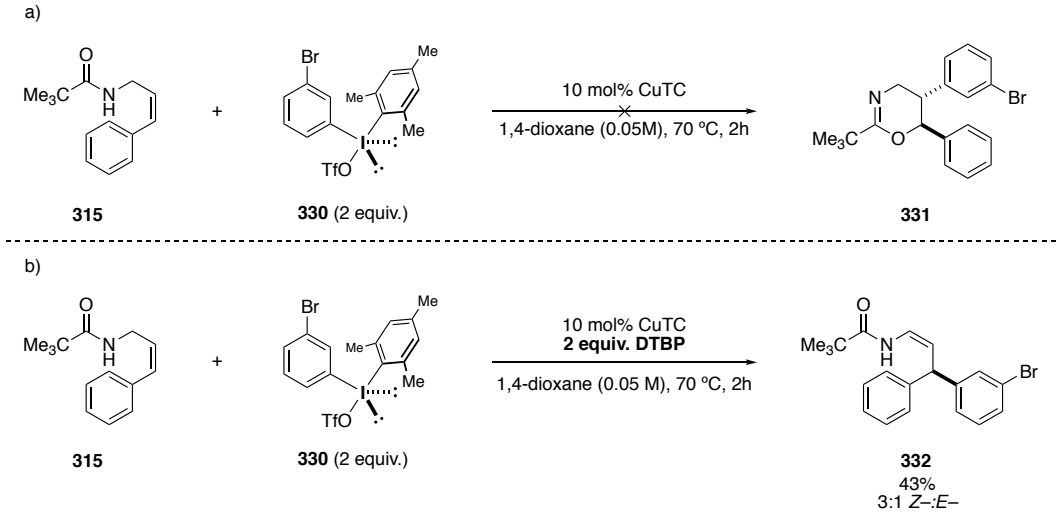
In 2012, Gaunt and co-workers described the reaction of allylic amides with diaryl- and alkenyl(aryl)iodonium triflates to furnish a range of oxazine products (Scheme 68).[157]



Scheme 68 – Gaunt's copper-catalysed oxazine formation from allylic amides with iodonium salts[157]

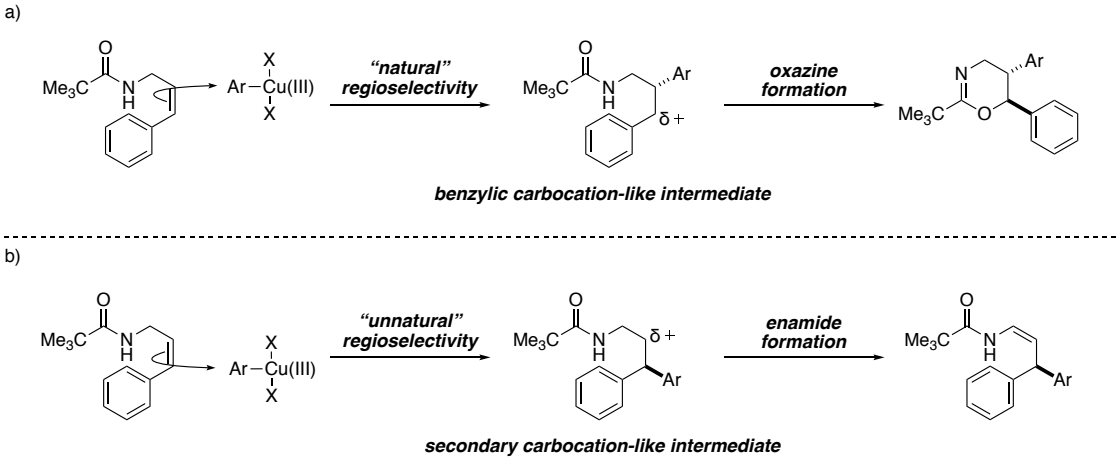
During the development of this alkene *oxy*-arylation reaction, Elise Cahard noted that no reaction was observed between phenyl substrate **315** and *meta*-bromophenyl iodonium triflate **330** (Scheme 69a).

Interestingly, the same reaction performed in the presence of the sterically-congested base 2,6-di-*tert*-butylpyridine (DTBP) led to the formation of a cis/trans mixture of enamide **332** (Scheme 69b).[162]



Scheme 69 – Reactivity of allylic amide **315** with iodonium salt **330** in a) absence and b) presence of 2,6-di-*tert*-butylpyridine (DTBP)[162]

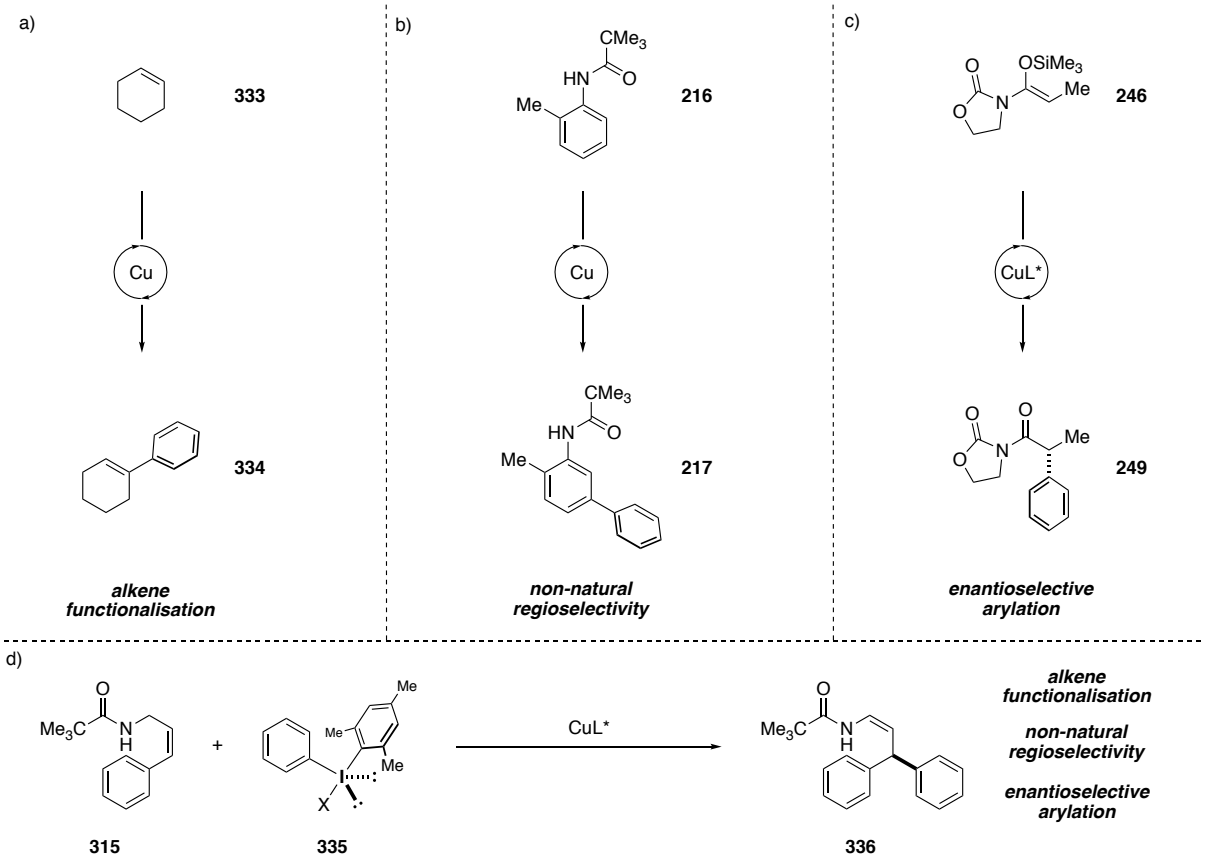
As was discussed in section 1.5.5, carbocation-like behaviour has been observed throughout Gaunt's investigations into copper catalysed alkene functionalisation processes using iodonium salts. Consistent with such a picture, the formation of oxazine products can be rationalised through a benzylic carbocationic intermediate (Scheme 70a). However, the production of enamide product **332** corresponds to a reversal in the expected regioselectivity of the alkene arylation, implying the preferential formation of a secondary carbocation-like intermediate (Scheme 70b).



Scheme 70 – a) expected arylation pathway, proceeding *via* the most stabilised carbocation to give oxazine formation; b) unexpected arylation towards the enamide, by analogy proceeding *via* a secondary carbocation

The observed non-natural regioselectivity indicates that alkene functionalisation under a copper/iodonium salt manifold is more complex than was previously imagined. In analogy with the

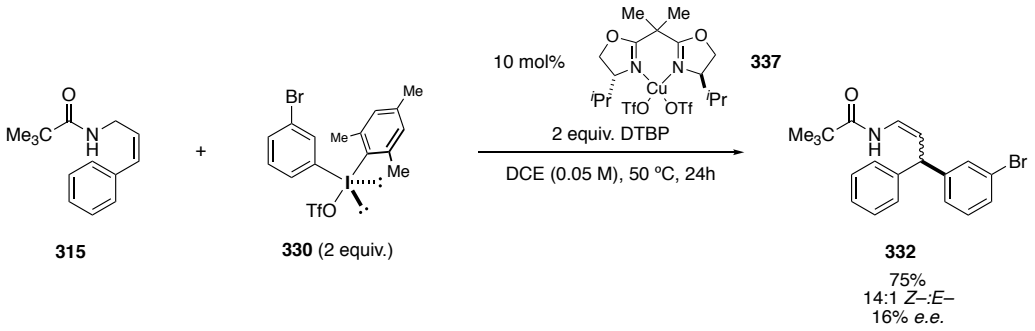
meta-arylation of pivanilides (Scheme 39, introduction), the formation of the enamide product can be attributed to the directing ability of the carbonyl moiety. It was questioned whether this non-natural alkene functionalisation process could be made enantioselective, merging three distinct concepts in high-valent copper catalysis (Scheme 71).



Scheme 71 – a) Gaunt's copper-catalysed arylation of alkenes;[155] b) Gaunt's *meta*-selective arylation of pivanilides;[126] c) Gaunt's enantioselective arylation of silylketinimides;[138] d) conceptual union of copper-catalysed alkene functionalisation, non-natural regioselectivity and enantioselective arylation chemistry

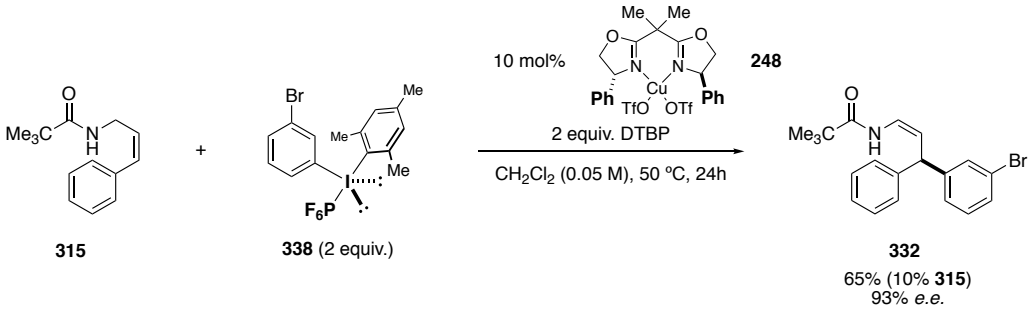
2.3 Initial Investigations

Previous work conducted as a part III student provided proof of concept for the enantioselective arylation of allylic amide substrate **315**. Conditions were identified to furnish diarylated enamide product **332** in 75% yield, high Z-selectivity and in 16% *e.e.* (Scheme 72).



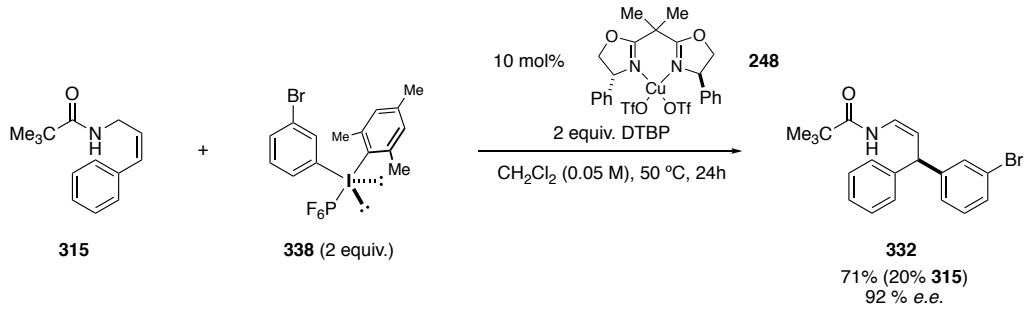
Scheme 72 – Initial enantioselective conditions for the formation of enamide **332** (NMR yield with 1,3,5-trimethoxybenzenetricarboxylate)

Subsequently, Elise Cahard applied the reagent combination used in MacMillan's silyl ketinimide arylation to the enamide formation process.[139] Pleasingly, the use of hexafluorophosphate salt **338** with catalyst complex **248** was observed to generate enamide **332** in 65% yield and 93% *e.e.* (Scheme 73).



Scheme 73 – Second-generation enantioselective conditions for the formation of enamide **332** (NMR yield with 1,3,5-trimethoxybenzenetricarboxylate) – Elise Cahard

Large variability in the yield of this enamide formation reaction was recorded. Subsequent investigations indicated that freshly prepared reagents were required in order to achieve reproducible results. Accordingly, the reaction was performed with fresh substrate, iodonium salt, catalyst complex and distilled di-*tert*-butylpyridine to give the product in a reliable 71% yield and 92% *e.e.* (Scheme 74).



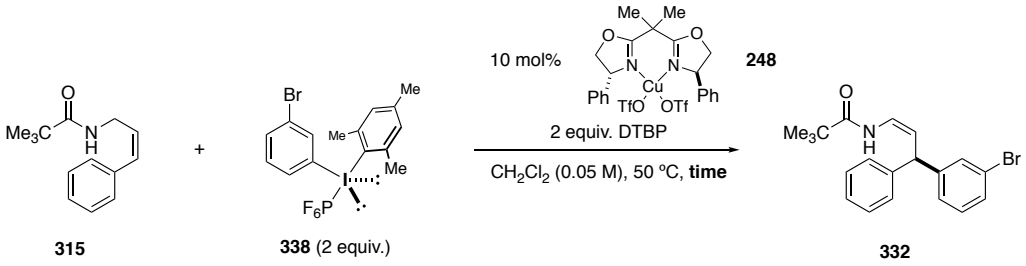
Scheme 74 – Enamide **332** formation under controlled conditions (NMR yield with 1,3,5-trimethoxybenzenetricarboxylate)

2.4 Further Reaction Optimisation

Following the observation of high enamide *e.e.* with the combination of allylic amide **315**, hexafluorophosphate iodonium salt **338** and catalyst **248**, Elise Cahard investigated other reaction parameters. Her studies included screens of bases and solvents, variation in the stoichiometries of the copper pre-catalyst solution, variation in the ratio of starting material to iodonium salt, and changes in the non-transferring aryl-group of the iodonium salt. No improvements were observed throughout these investigations. Further optimisation studies were then carried out on uninvestigated reaction parameters.

2.4.1. Enamide stability and reaction time

The effect of increasing the length of the reaction time was first probed (Table 4). No improvement in yield was achieved by quenching the reaction after 28 hours compared with a 24-hour reaction-time. Incomplete mass balance was observed with extended exposure.

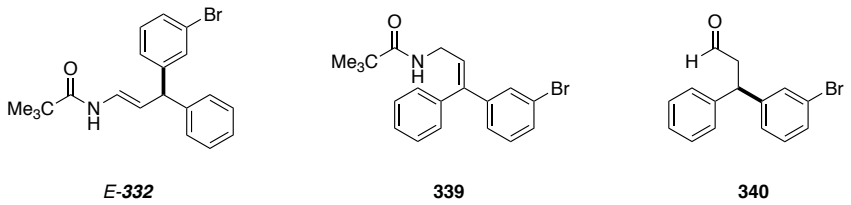


Entry	Reaction time	Yield / %[a,b]
1	24 hours	70 (30)
2	28 hours	70 (18)

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material.

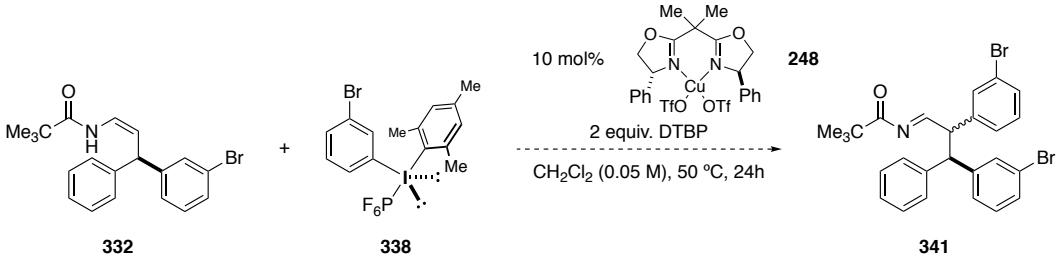
Table 4 – Investigation into the effect of increasing the reaction time

^{1}H NMR analysis of the crude enamide-formation reaction reveals the presence of thermal rearrangement product *E*–**332** (<5%) and traces of what are thought to be alkene **339** and aldehyde **340** (Figure 6). It is proposed that the remainder of the mass may be lost through a second arylation at the α-position of the enamide (Scheme 75). Evidence for such reactivity is provided by Pannecoucke, Gillaizeau and Kesavan's observation that cyclic enamides react with iodonium salts under copper-catalysed arylation conditions.[136,137]



E-332 **339** **340**

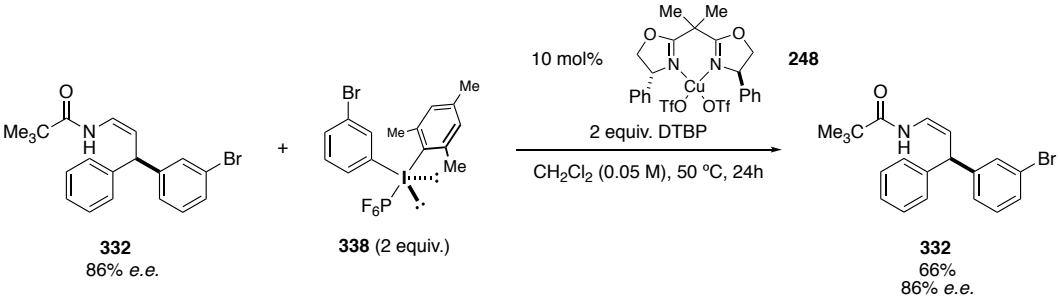
Figure 6 – Side products of enamide formation reaction



332 **338** **341**

Scheme 75 – Plausible over-reaction of enamide **332**

Separately, a sample of the purified product **332** was re-exposed to the reaction environment to test the stability of the enamide to the reaction conditions. This experiment gave 66% product recovery after 24 hours (Scheme 76). Although tentative evidence for the formation of a *ter*-aryl species was observed by LCMS analysis, no such derivatised product could be isolated or observed by NMR. It was concluded that a 24-hour reaction-time provided optimum conversion of allylic amide to enamide whilst minimising product decomposition.



332
86% *e.e.*

338 (2 equiv.)

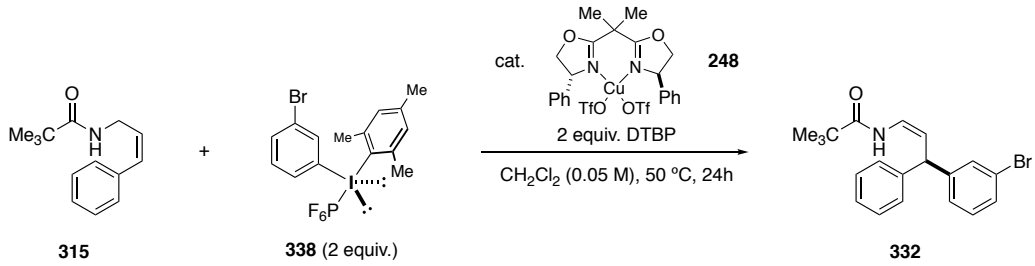
332
66%
86% *e.e.*

Scheme 76 – Investigation into the stability of enamide **332** on exposure to the reaction conditions

2.4.2. Catalyst loading

The effect of varying the amount of catalyst was next tested (Table 5). A reduced catalyst-loading gave low starting material conversions and therefore poor product yields (entry 1, 5 mol% catalyst, 60% **315** remaining). Enamide production was observed to more than double on increasing the loading of **248** to 10 mol% (entry 1 *vs.* entry 2 – 30 to 70% yield). Little further improvement was seen with a catalyst loading of 20 mol% (75% yield, entry 3) and the yield of the reaction dropped on the addition of 50 mol% **248** (entry 4). Introduction of a second equivalent of catalyst to the reaction mixture after 14 hours appeared to have no effect on the yield or conversion of the transformation (entry 5 *vs.* entry 2).

Catalyst loading was maintained at 10 mol% as the slight increase in yield observed with 20 mol% copper was not sufficiently significant to justify using twice the amount of the pre-catalyst.



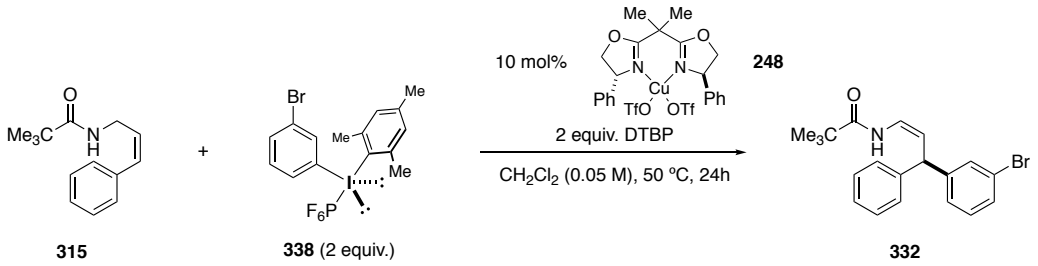
Entry	Catalyst loading / mol%	Yield / %[a,b]	*e.e.* / %[c]
1	5	30 (60)	92
2	10	70 (10)	93
3	20	75 (05)	92
4	50	50 (20)	88
5	10 + 10[d]	70 (10)	93

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] added after 14 hours

Table 5 – Effect of catalyst loading on the reaction

2.4.3. Pre-stirring studies

Qualitative observations indicated that the enamide-formation reaction undergoes a lag-phase prior to the generation of product, attributable to a slow catalyst activation process. It was questioned whether the yield of the reaction could be improved by mixing the pre-catalyst with individual reagents before heating as normal (Table 6), hopefully leading to more rapid catalyst activation. However, as all reactions gave yields and enantioselectivities comparable with, or worse than, the control reaction (entry 1), little advantage from pre-stirring the reaction components with the pre-catalyst was apparent. Despite the lack of improvement, it was interesting to note that pre-stirring the catalyst with the substrate (entries 2 and 4) resulted in lower conversion of starting material. In contrast, a relative increased consumption of starting material was observed when the iodonium salt was pre-stirred with the catalyst (entries 3 and 5). These results could indicate that the allylic amide substrate inhibits the catalyst activation process.



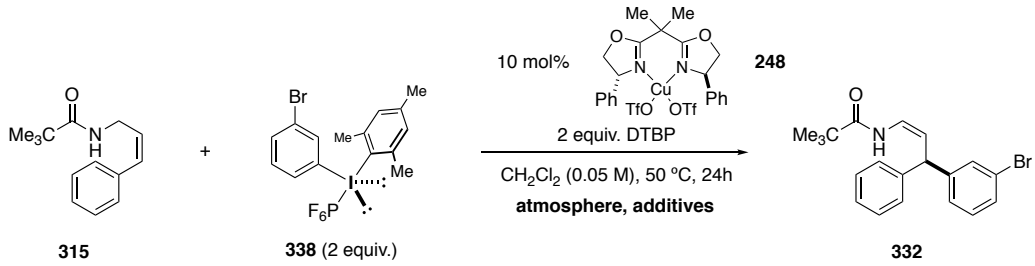
Entry	Prestirred components[a]	Yield / %[b,c]	*e.e.* / %[d]
1	–	77 (05)	93
2	**248** and **315**	60 (20)	93
3	**248** and **338**	78	94
4	**248**, **315** and DTBP	70 (20)	92
5	**248**, **338** and DTBP	75 (05)	91

[a] Pre-stirred at room-temperature for 2 hours before the addition of the remainder of the reagents and stirring for 24 hours; [b] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [c] bracketed quantity denotes remaining starting material; [d] *e.e.* determined by chiral HPLC assay

Table 6 – Assessment of the effect of pre-stirring reaction components

2.4.4. Atmosphere and radical activity

In order to test for possible oxygen sensitivity, a control reaction was performed alongside two further reactions (Table 7, entries 1–3). The first of these reactions was carried out under an atmosphere of argon; the second was performed in freeze-pump-thawed degassed dichloromethane and under an atmosphere of nitrogen. Whilst the use of both standard nitrogen and argon atmospheres gave similar results (entries 1 and 2), degassed solvent gave reduced substrate conversion (entry 3). This poor result led to speculation that the solvent of the standard reaction may contain dissolved oxygen. It was considered that associated radical behaviour might promote the reaction. The process was therefore performed both under an oxygen headspace (entry 4) and with the radical trap 1,1-diphenylethylene (entry 5). Whilst, the oxygen atmosphere gave a poor yield and low starting material conversion, the use of the radical trap gave a similar yield to the control reaction (70%). It was concluded that oxygen and any resulting radical behaviour were not important for reactivity and that use of a simple nitrogen atmosphere was sufficient for good results.



315 338 (2 equiv.) 332

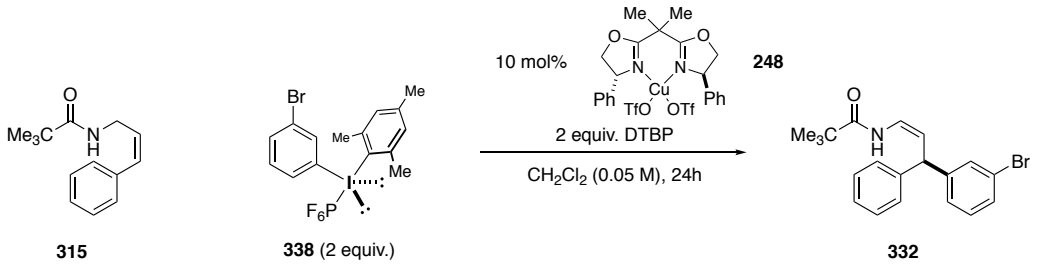
Entry	Conditions	Yield / %[a,b]	*e.e.* / %[c]
1	N_2 atmosphere	72 (04)	n.d.
2	Ar atmosphere	72 (03)	n.d.
3[d]	N_2 atmosphere, degassed CH_2Cl_2	60 (20)	93
4	O_2 atmosphere	57 (20)	92
5[e]	N_2 atmosphere, 1,1-DPE (4 equiv.)[d]	70 (10)	92

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] freeze-pump-thaw degassed; [e] DPE = diphenylethylene

Table 7 – Effects of varying atmosphere, degassing solvent and introduction of a radical trap

2.4.5. Temperature

The effect of both increasing and decreasing the reaction temperature was next examined (Table 8). It was thought that a higher reaction rate could be attained by increasing temperature, maximising product yields within twenty-four hours. Similarly, it was considered that lowering the reaction temperature may improve catalyst stability, allowing for a greater number of catalyst turn-overs. However, both increased and decreased reaction temperatures gave reduced yields relative to results observed at 50 °C. The reaction run at 70 °C gave poor mass balance and low *e.e.*, whilst the 40 °C process gave poor conversion and still only 80% mass balance. Temperature was not investigated further.



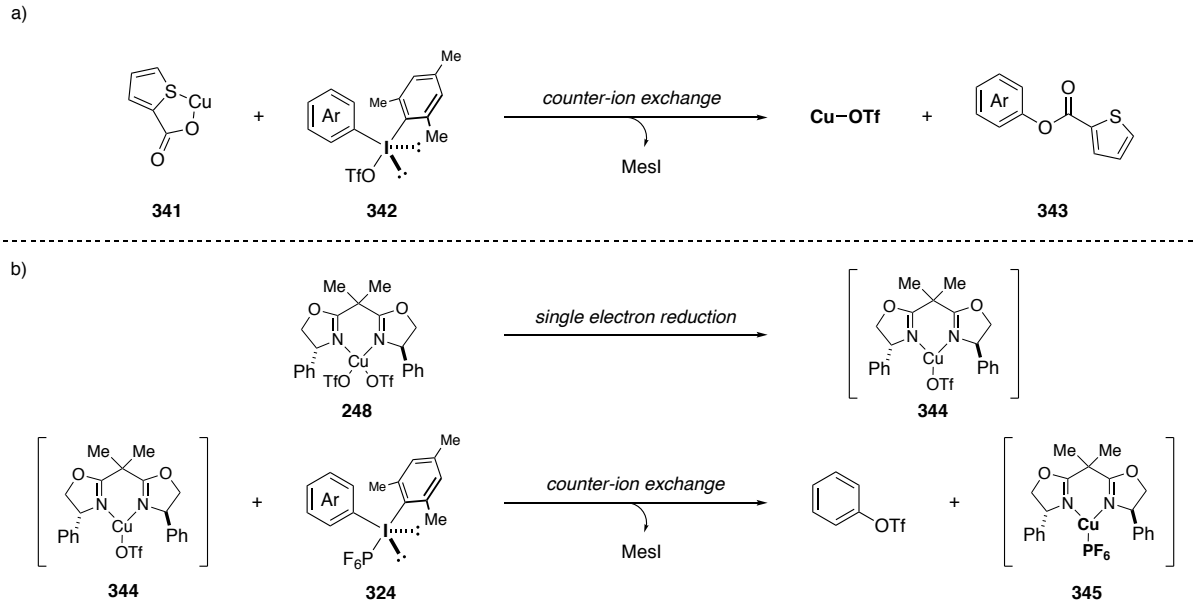
Entry	Temperature / °C	Yield / %[a,b]	*e.e.* / %[c]
1	70	45 (20)	65
2	40	50 (30)	91

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay

Table 8 – Effect of varying temperature

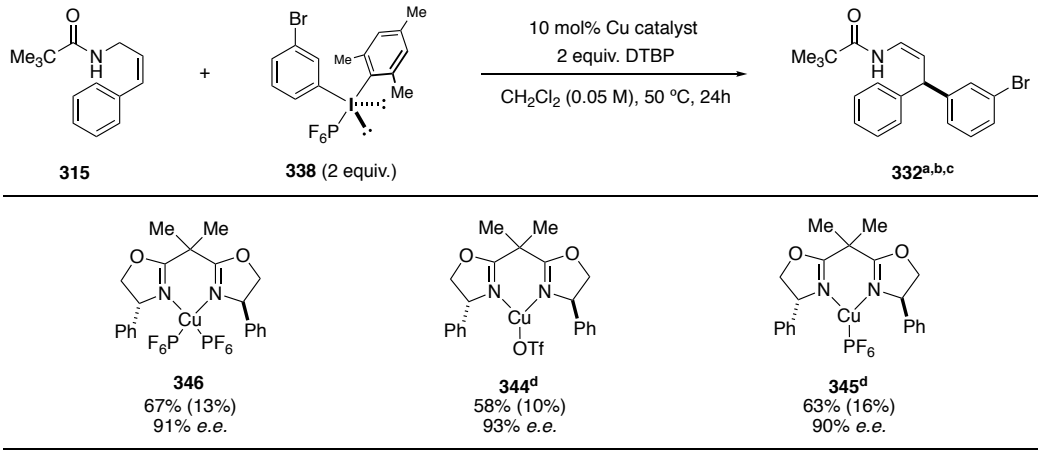
2.4.6. Catalyst counter-ion

It was noted by Robert Phipps, a former PhD student in the Gaunt laboratory, that reactions employing diaryliodonium triflates catalysed by copper(I)-thiophene-2-carboxylate (CuTC, **341**) gave catalytic amounts of phenolic ester **343**. The generation of **343** was proposed to give concomitant production of copper(I) triflate, then acting as the active catalyst in the system (Scheme 77a).



Scheme 77 – a) Counterion exchange from CuTC **341** to CuOTf, b) hypthothetical generation of catalytic hexafluorophosphate adduct **345**

It was therefore hypothesised that the active allylic amide arylation catalyst would be the ligand-bound Cu(I) hexafluorophosphate species **345**, formed by single-electron reduction of Cu(II) triflate species **248** followed by a counter-ion exchange process (Scheme 77b). It was thought that higher yields may be achieved by removing the need for the copper centre to undergo either one or both activation processes. Accordingly, use of the three Cu(I) and Cu(II) triflate and hexafluorophosphate (pre-)catalysts shown below in Table 9 were assessed for competence in the allylic amide arylation process. Disappointingly, all reactions furnished the enamide product in similar yields, conversions and *e.e.*s to the standard catalytic system. Despite providing no improvement, it was interesting to observe these reactions to give such similar yields and levels of enantioselectivity, providing tentative evidence that the active catalyst is the same in all cases. Optimisation studies were continued with Cu(II) pre-catalyst **248** due to its relative ease of handling and preparation.

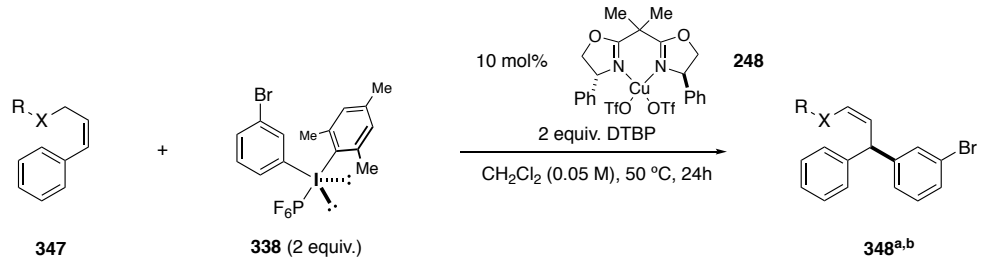


[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] performed by Elise Cahard

Table 9 – Alternative carbonyl-bearing substrates tested in the reaction

2.4.7. Use of alternative substrates

It was next considered whether the amide group of the substrate could be exchanged for a different carbonyl-bearing functionality. Four alternative substrates, predicted to direct functionalisation to the less nucleophilic alkene position were therefore prepared and tested under the arylation conditions (Table 10). None of the analogues provided any enamide product. The more electron-rich substrates, urea **350** and benzoyl amide **351**, were unstable to the reaction conditions whilst the more electron-deficient ester **349** and phthalimide **352** were inert. It was concluded that a pivaloyl amide group was crucial for reactivity to give enamide formation.



349	350	351	352[c]
0 (100)	0 (74)	0 (65)	0 (100)

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] Substrate 90% purity – contaminated with corresponding alkane

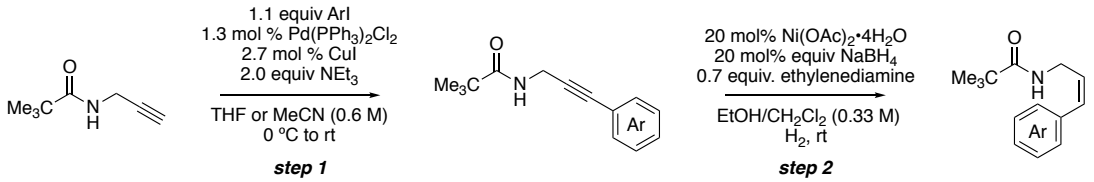
Table 10 – Alternative carbonyl-bearing substrates tested in the reaction

2.4.8. Overview

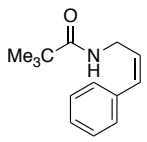
No significant increase in yield was recorded throughout these optimisation investigations. A balance between reaction conversion and product stability was observed, with the process apparently sensitive to parameters including time, temperature and catalyst-loading. It was concluded that the reaction was not easily controlled by external parameters beyond the use of a specific catalyst and iodonium salt combination. As the observed yields of approximately 70% with accompanying excellent enantioselectivities were considered acceptable for the arylation process, the scope of the allylic amide functionalisation procedure was next evaluated.

2.5 Reagent Synthesis

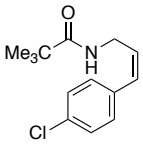
Attention was directed towards the generation of a range of allylic pivalamide substrates and diaryliodonium hexafluorophosphate salts suitable for future investigations. Twelve allylic amide substrates were prepared from propargylic amide **353** by a two-step reaction sequence comprising a Sonogoshira coupling and *cis*-selective alkyne reduction (Table 11).[157] Separately, ten diaryliodonium hexafluorophosphate salts were generated in good yields from the corresponding triflate or tetrafluoroborate salt through an ion exchange process (Table 12).



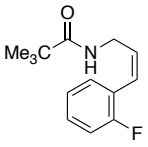
353 **354** **355**



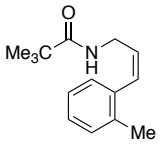
315
step 1: 71%
step 2: 89%



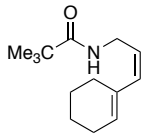
356
step 1: 77%
step 2: 78%



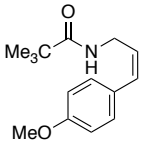
357[a]
step 1: 75%
step 2: 81%



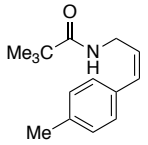
358[a]
step 1: 83%
step 2: 83%



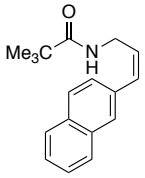
359[a]
step 1: 85%
step 2: 64%



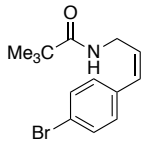
360
step 1: 86%
step 2: 78%



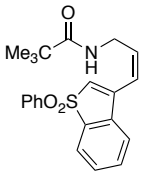
361
step 1: 72%
step 2: 58%



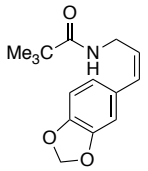
362
step 1: 82%
step 2: 78%



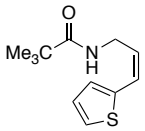
363
step 1: 81%
step 2: 59%



364[b]
step 1: 86%
step 2: 70%



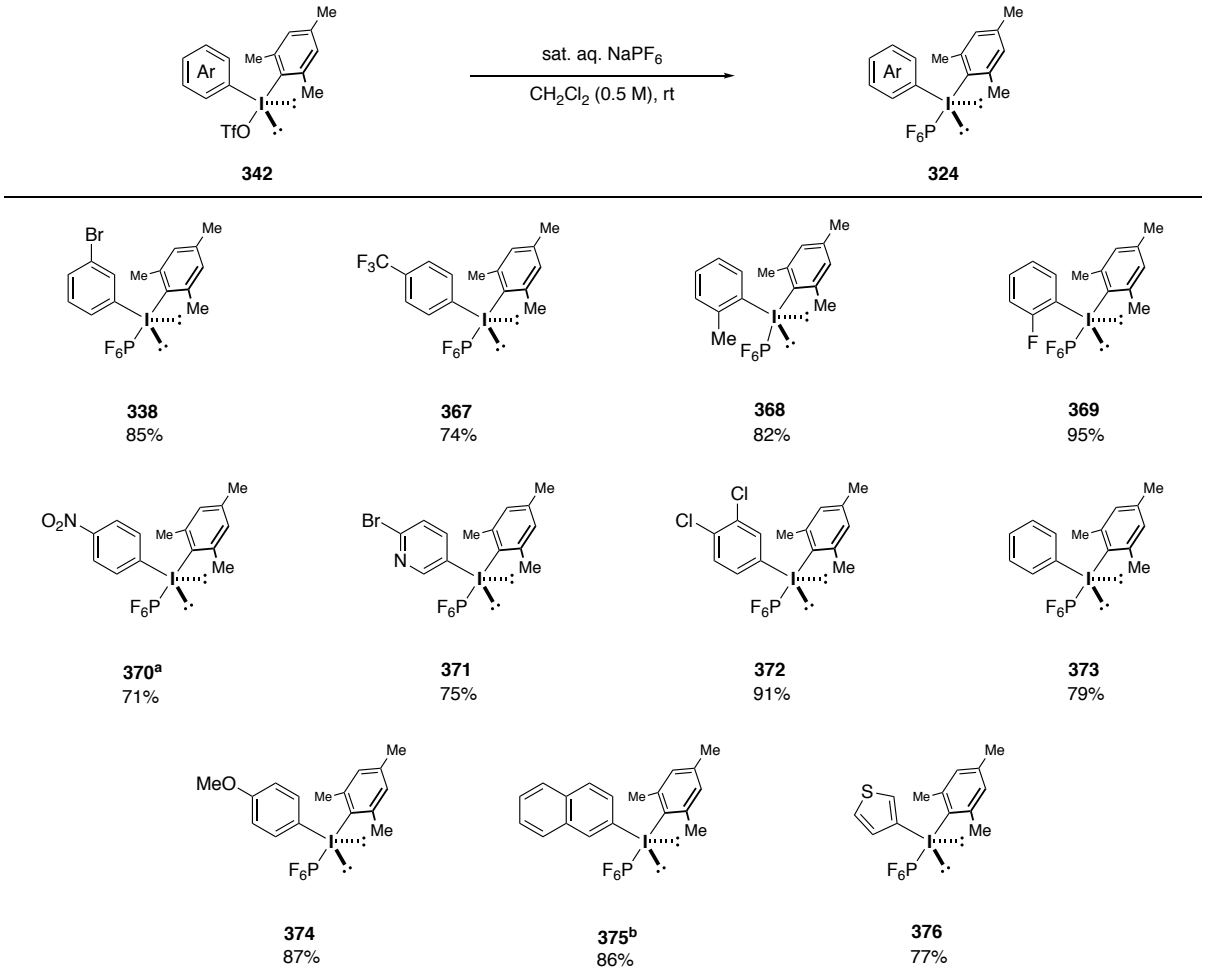
365
step 1: 76%
step 2: 81%



366
step 1: 74%
step 2: 69%

[a] performed by Elise Cahard; [b] reduction performed with 0.6 equiv. $Ni(OAc)_2•4H_2O$, 0.6 equiv. $NaBH_4$, 2.1 equiv. ethylenediamine

Table 11 – Two-step Sonogoshira coupling and *cis*-selective reduction procedure yielding *Z*-allylic amides



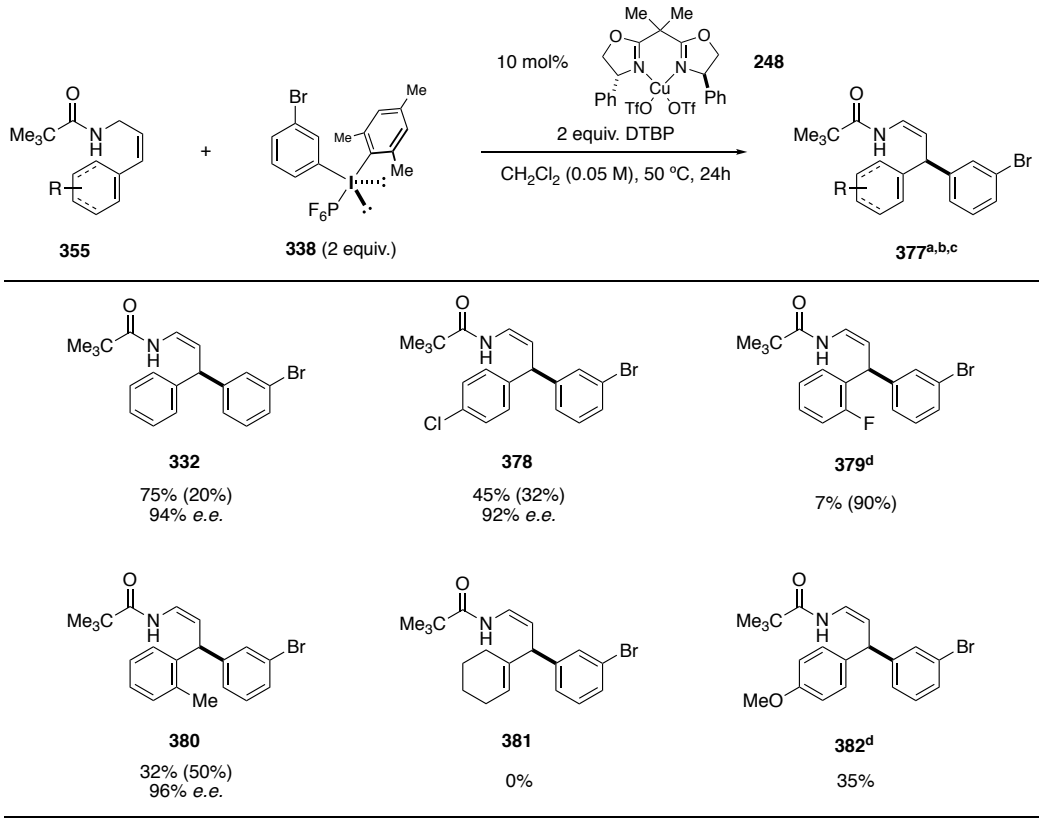
[a] performed by Elise Cahard; [b] from corresponding tetrafluoroborate iodonium salt

Table 12 – Synthesis of hexafluorophosphate iodonium salts by ion-exchange

2.6 Enamide Formation Scope Investigations

2.6.1. Initial studies

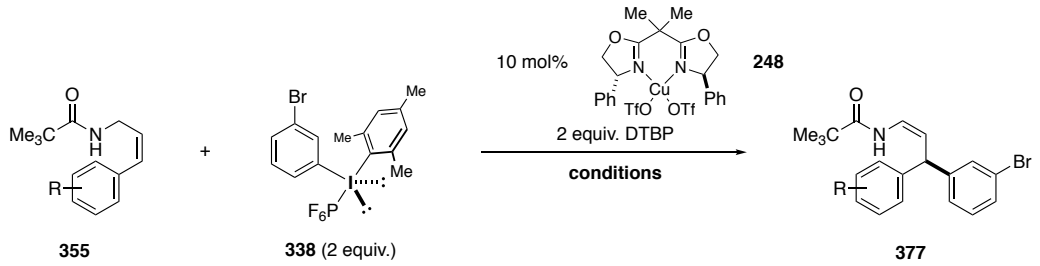
Six allylic amides were exposed to the optimised reaction conditions with iodonium salt **338** as a preliminary substrate scope (Table 13). Despite the observation of a good 75% yield for the control reaction (enamide **332**), all other substrates gave poorer yields of the corresponding products. The use of substrates **356–358** gave low conversions (32–90% starting material remaining), though excellent enantioselectivities were recorded for the formation of *para*-chlorophenyl and *ortho*-tolyl enamides **378** and **380** (92 and 96% *e.e.* respectively). Dienyl substrate **359** appeared unstable to the reaction conditions and gave no desired product. The electron-rich *para*-methoxyphenyl substrate **360** gave the desired enamide **382** in 35% NMR yield with no residual starting material. Disappointingly, this enamide product was found to be unstable to isolation.

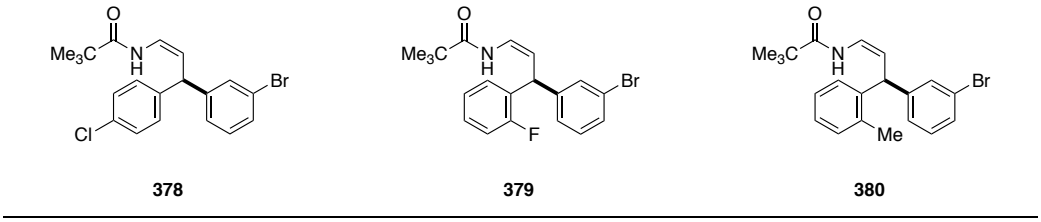


[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] *e.e.* could not be determined due to product instability

Table 13 – Initial investigation into the scope of the enamide formation process

A brief optimisation survey was carried out on the reactions giving enamide products **378–380** (Table 14). Increasing the reaction time from 24 to 48 or 72 hours led to higher yields and improved conversions in all cases (entries 1–3). However, this advantageous increase in yield was countered by a universal drop in *e.e.* (60–66% *vs.* >90%). Likewise, increasing the reaction temperature from 50 to 60 °C (entries 4–6) gave higher starting material consumption but significantly reduced enantioselectivities (45, 15 and 35% *e.e.* respectively). Finally, increasing the reaction concentration from 0.05 M to 0.1 M (entries 7–9) gave little change in the yield or *e.e.* of the enamide products. As such, it appears from these studies that the original reaction conditions provide the best trade-off between yield and enantioselectivity. Further, the lack of improvement observed throughout this investigation reinforces our previous conclusion that enamide formation cannot be readily ameliorated by deviating from the standard reaction conditions of heating at 50 °C for 24 hours at a 0.05 M concentration.





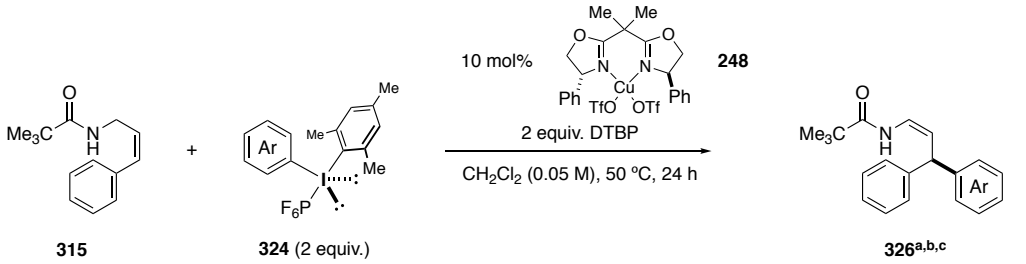
Entry	Product	Conditions[a]	Yield / %[b,c]	*e.e.* / %[d]
1	**378**	**A**	55	60
2	**379**	**A**[e]	40 (42)	65
3	**380**	**A**	47	66
4	**378**	**B**	45 (15)	45
5	**379**	**B**	20 (70)	15
6	**380**	**B**	24 (33)[f]	35
7[g]	**378**	**C**	42 (29)	93
8[g]	**379**	**C**	12 (72)	89
9[g]	**380**	**C**	34 (51)	97

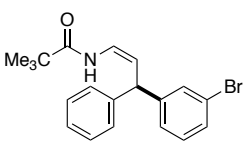
[a] conditions: **A** – CH_2Cl_2 (0.05 M), 50 °C, 48 h; **B** – CH_2Cl_2 (0.05 M), 60 °C, 24 h; **C** – CH_2Cl_2 (0.1 M), 50 °C, 24 h; [b] yields determined by ^1H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [c] bracketed quantity denotes remaining starting material; [d] *e.e.* determined by chiral HPLC assay; [e] 72 hours; [f] 10% *trans*-enamide and 8% oxazine additionally observed; [g] isolated yields

Table 14 – Investigations into the effect of reaction length, temperature and concentration on the yields and *e.e.* of enamides **378–380**

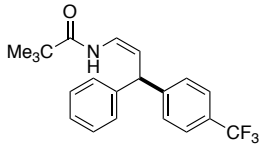
Attention was next turned to the iodonium salt scope of the enamide generation procedure. Initial investigations employed electron-poor and sterically-encumbered diaryliodonium salts as these are reported to be poorly-tolerated in the racemic oxazine-formation reaction (Table 15).[157,162] Beyond the use of the standard *meta*-bromophenyl iodonium salt **338**, giving the corresponding enamide in 75%

yield and 94% *e.e.*, three further iodonium salts gave appreciable product yields. *Para*-trifluoromethylphenyl enamide **383** was formed in 58% yield and in high enantioselectivity (92% *e.e.*) whilst the *ortho*-tolyl and *ortho*-fluorophenyl enamides were produced in 20% and 35% yield respectively. Interestingly, the generation of *ortho*-tolyl enamide **384** is accompanied by the production of 8% of the corresponding oxazine, indicating some mechanistic cross-over in the reaction. Neither *para*-nitrophenyl nor pyridinyl-iodonium salts were tolerated under the reaction conditions.

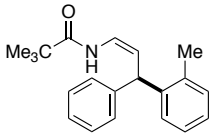




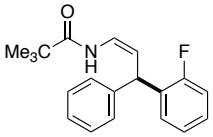
332
75% (20%)
94% *e.e.*



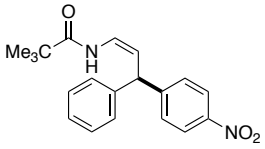
383
58% (25%)
92% *e.e.*



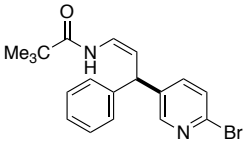
384[d]
20% (60%)



385
35% (55%)



386[e]
3% (73%)

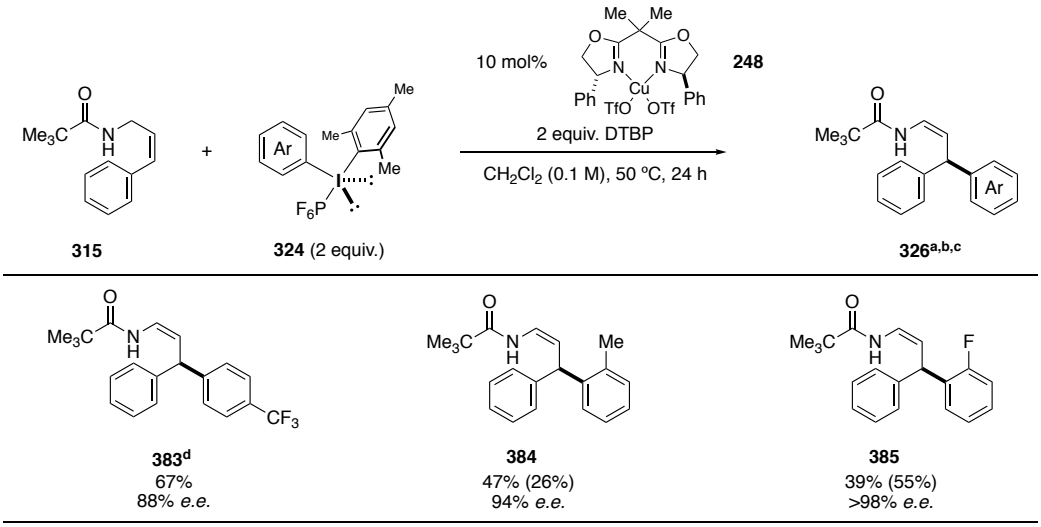


387
0% (100%)

[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] 8% corresponding oxazine observed; [e] 72 hour reaction time.

Table 15 – Initial evaluation of the iodonium salt scope of the enamide formation

It was discovered that increasing the concentrations of the reactions giving enamides **383–385** gave improved conversions and product yields (Table 16, 0.1 M). An 11% increase in yield was observed for *para*-trifluoromethylphenyl enamide **383** with only a slight drop in *e.e.* relative to the comparative reaction at 0.05 M. *Ortho*-tolyl enamide **384** was produced in 47% yield and 94% *e.e.* with no competitive formation of the undesired oxazine side-product. A small increase in yield was also observed for *ortho*-fluorophenyl enamide **385**, giving the product in 39% yield and very high enantioselectivity.

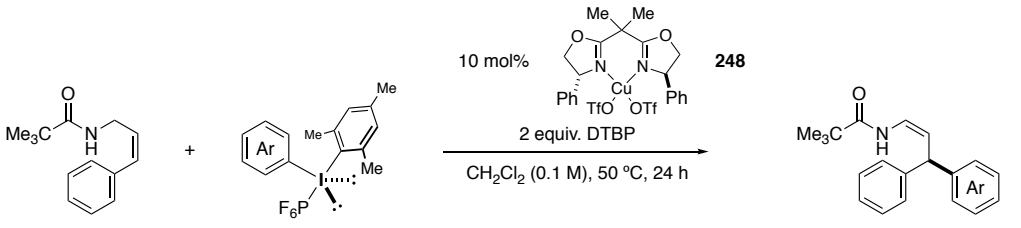


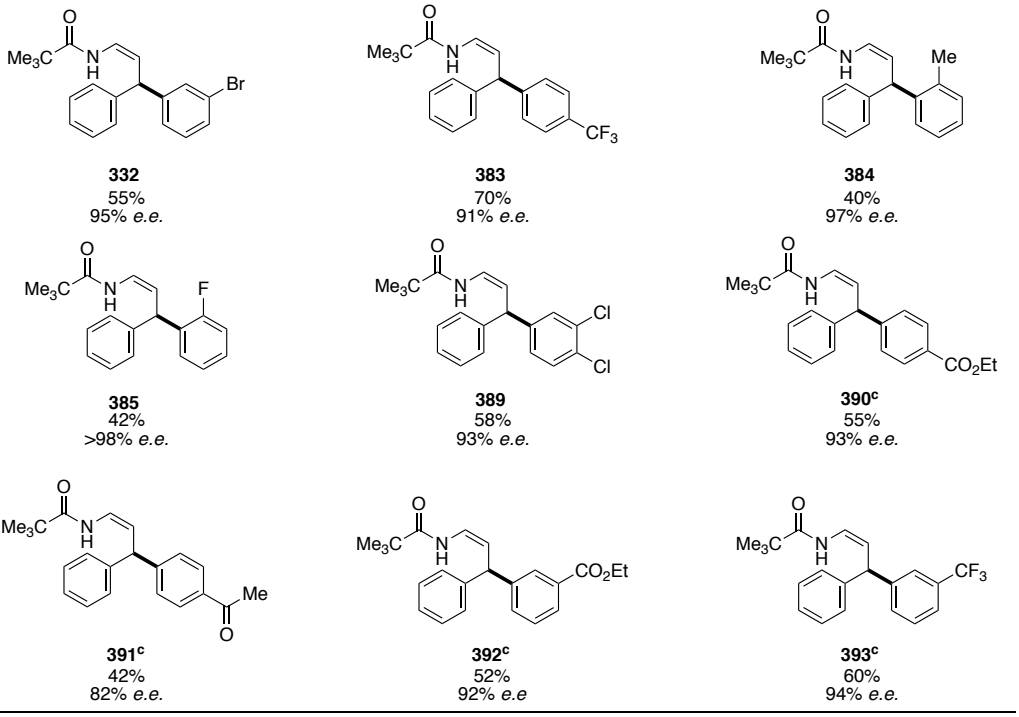
[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes remaining starting material; [c] *e.e.* determined by chiral HPLC assay; [d] 5% *trans*-enamide observed

Table 16 – Initial evaluation of the iodonium salt scope of the enamide formation

2.6.2. Isolated reaction scope

In collaboration with Elise Cahard, the scope of the reaction was investigated on a 0.5 mmol scale with the isolation of the product enamides. Attention was first directed towards variation in the iodonium salt component of this alkene functionalisation transformation (Table 17). It was observed that moderate to good yields (40–70%) are achieved with iodonium salts bearing electron-withdrawing groups with Hammett σ-values in the range of 0.6–0.3. Enantioselectivities were generally recorded to be excellent, giving >90% *e.e.* in all cases except for the formation of *para*-acetylphenyl enamide **391** (82% *e.e.*). Both σ- and π-electron-withdrawing groups are tolerated in the *meta*- and *para*-positions of the transferred aryl ring. *Ortho*-substitution of the transferred aryl-group is also tolerated, with enamide **384** generated in 40% yield despite the electron-rich nature of the iodonium salt employed.



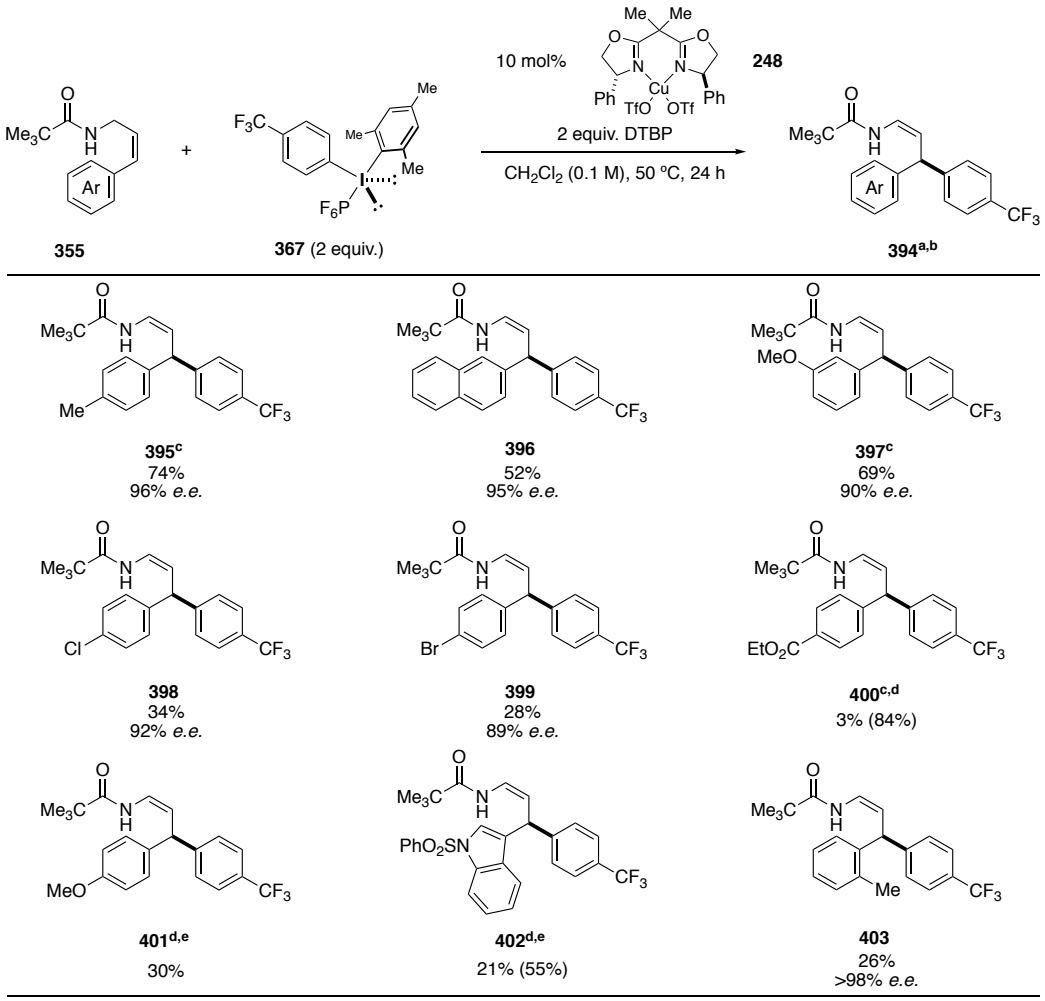


[a] isolated yields; [b] *e.e.* determined by chiral HPLC assay; [c] performed by Elise Cahard

Table 17 – Isolated iodonium salt scope of the enamide formation reaction

The scope of the enamide formation reaction towards variation in the allylic amide substrate was next investigated (Table 18). *Para*-trifluoromethylphenyl iodonium salt **367** was employed in these studies as it provided the greatest isolated yield in the iodonium salt scope above. Interestingly, whilst levels of enantioselectivity are consistently high, there appears to be a relationship between the electronic properties of the starting materials and the yields of the reactions. Electron-neutral substrates (Hammett σ-parameters ~0 ± 0.2) gave the best results in the study, with the *para*-tolyl, 2-napthyl and *meta*-methoxyphenyl substituted enamides, **395**, **396** and **397** formed in the yields in the range of 52 to 74%. More electron-poor substrates gave lower yields, attributable to reduced nucleophilicity of the alkene. Such an effect is illustrated by inspecting the trend of reactivity from *para*-chloro- and *para*-bromophenyl substrates **356** and **363** (σ 0.37 and 0.39, giving 34 and 28% enamide formation respectively) to *para*-ester-substituted substrate (σ 0.45, only trace enamide formation). Intriguingly, more electron-rich substrates such as the *para*-methoxyphenyl- (σ –0.27) and indole species appear to give enamide

formation but unstable products. Finally, *ortho*-substitution of the substrate (product **403**) gives low yields of enamide (26%) but very high levels of enantioselectivity (>98% *e.e.*).



[a] isolated yields; [b] *e.e.* determined by chiral HPLC assay; [c] performed by Elise Cahard; [d] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate, bracketed quantity denotes % residual starting material; [e] enamide product unstable to isolation

Table 18 – Substrate scope of the enamide formation transformation

Brominated enamide **399** was crystalline, allowing the determination of the absolute configuration of this compound by X-ray diffraction (Figure 7). The crystal structure revealed a unit cell of two *S*-configured enamide molecules. The remainder of the enamide products were configurationally assigned by analogy.

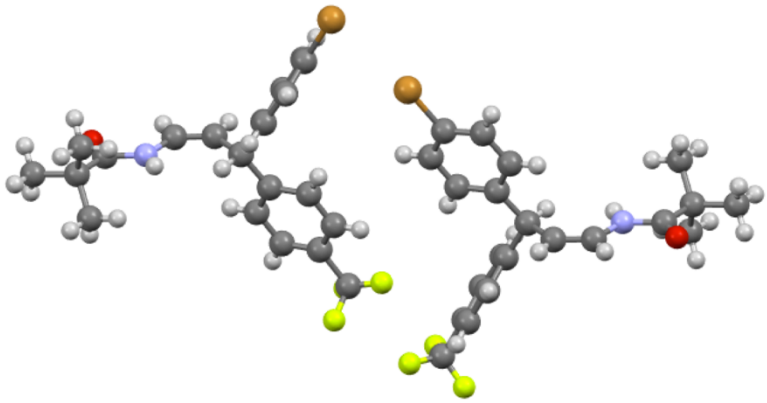
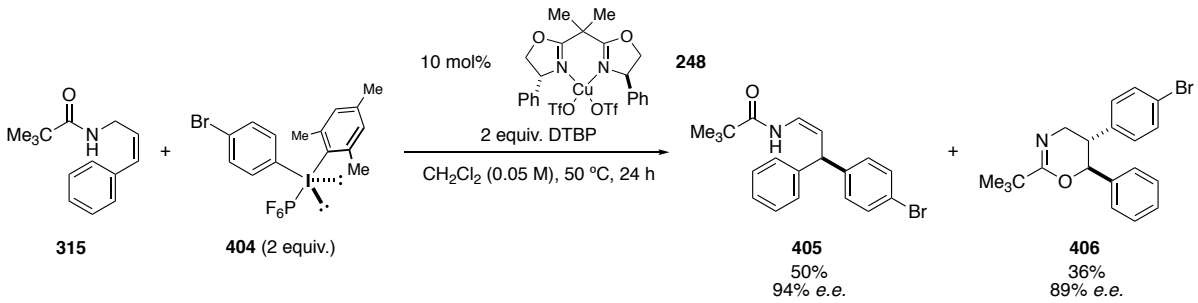


Figure 7 – X-ray crystal structure of enamide **399**

2.7 Oxazine Formation

2.7.1. Discovery

Elise Cahard noted that a 3:2 mixture of enamide **405** and oxazine **406** was produced from the combination of *para*-brominated iodonium salt **404** and the standard allylic amide substrate **315** (Scheme 78). Most interestingly, both products were formed in high *e.e.*, indicating the enantioselective arylation strategy to be extendable to oxazine formation.

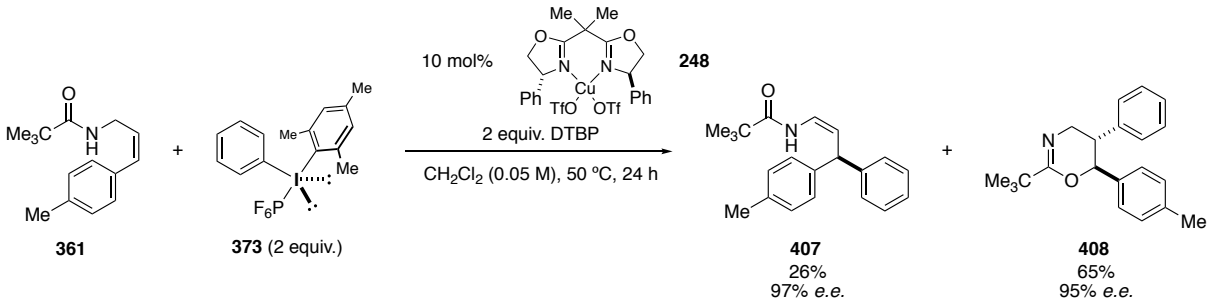


[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] *e.e.* determined by chiral HPLC assay

Scheme 78 – Regiodivergent arylation with iodonium salt **404** to give enantioenriched products – Elise Cahard

As enamide formation appears to be favoured with electron-poor iodonium salts, the above product mixture was attributed to the relatively poor electron-withdrawing ability of the *para*-bromophenyl group (Hammett σ-value 0.23). This result suggested that the use of a more electron-rich iodonium salt would further bias the reaction towards oxazine formation. Such a hypothesis was tested by exposing phenyl(mesityl)iodonium hexafluorophosphate **373** to the reaction conditions with *para*-tolyl allylic amide **361** (Scheme 79). Pleasingly, it was observed that increased aryl electron-density did indeed favour *oxy*-arylation, with the transfer of a phenyl group (σ 0.0) giving predominant oxazine production

(65%) and minor enamide formation (26%). High product enantioselectivity was conserved, giving 97 and 95% *e.e.* for enamide and oxazine products respectively. The described arylation procedure therefore represents an enantioselective and regiodivergent alkene functionalisation reaction wherein the regioselectivity may be controlled by the electronic nature of the iodonium salt employed.

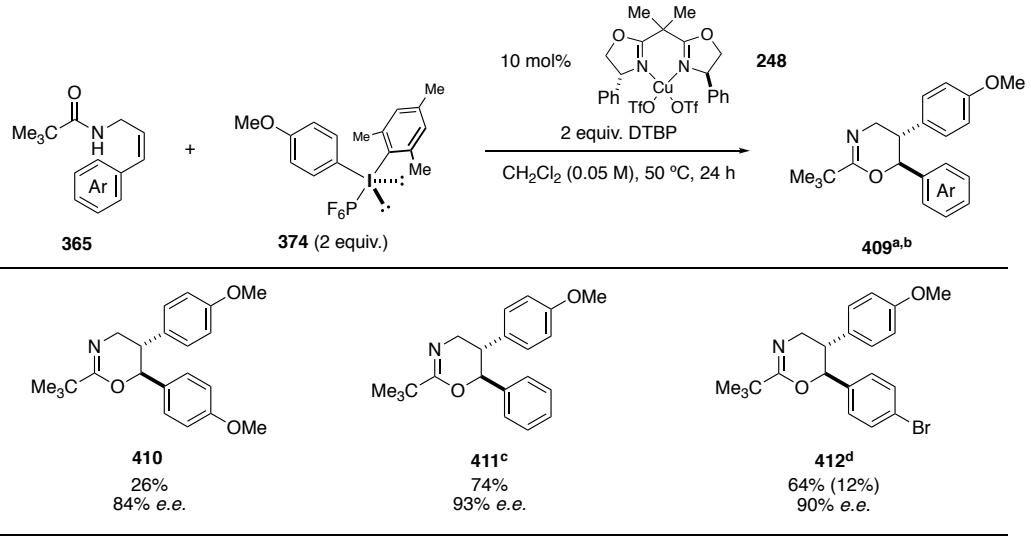


[a] yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] *e.e.* determined by chiral HPLC assay

Scheme 79 – Regiodivergent arylation with iodonium salt **373** to give enantioenriched products **407** and **408**

2.7.2. Substrate scope

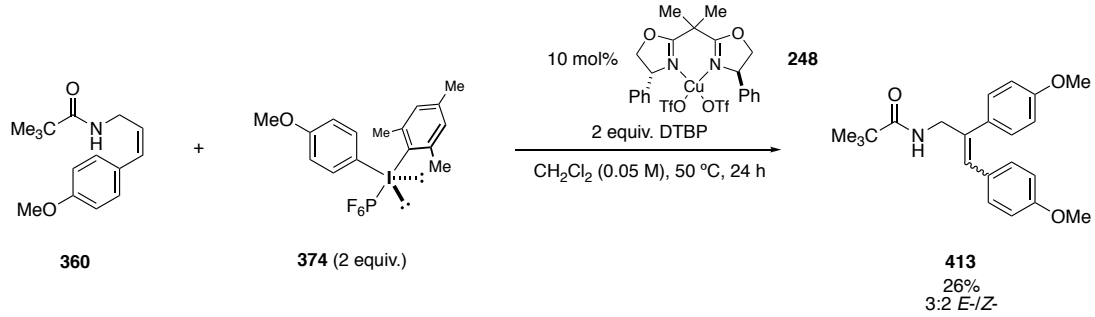
Attention was turned towards the application of the combination of allylic amides and electron-rich diaryliodonium salts towards the generation of a range of oxazine products in high *e.e.*. The substrate scope of this enantioselective *oxy*-arylation reaction was first examined by testing three substrates spanning Hammett σ-values in the range of −0.2 to 0.2 (Table 19). Oxazine formation was favoured with the use of the highly electron-rich *para*-methoxyphenyl iodonium salt **374**. Firstly, *para*-methoxyphenyl substrate **360** gave good starting material conversion but a low overall yield of oxazine **410** (26%) and a lower *e.e.* (84%) than has been previously observed. Secondly, the electron-neutral phenyl substrate **315** gave the desired product in a good 74% yield and in an excellent 93% *e.e.*. Thirdly, despite the observation of 12% residual starting material, the electron-deficient *para*-bromo substrate **363** gave good product yield and enantioselectivity following an extended reaction time of 43 hours (64% and 90% *e.e.*). As such, it is apparent that oxazine instability, good product yields and low starting material conversion are observed respectively with the use of electron-rich, electron-neutral and electron-poor substrates. This pattern replicates the reactivity seen with enamide formation (see Table 13).



[a] isolated yields, bracketed quantity denotes residual starting material; [b] *e.e.* determined by chiral HPLC assay; [c] performed by Elise Cahard; [d] Reacted for 43 hours – 2:1 ratio of oxazine product to starting material observed by ^{1}H NMR after 24 hours

Table 19 – Initial investigation into the tolerance of substrate electronics on oxazine formation

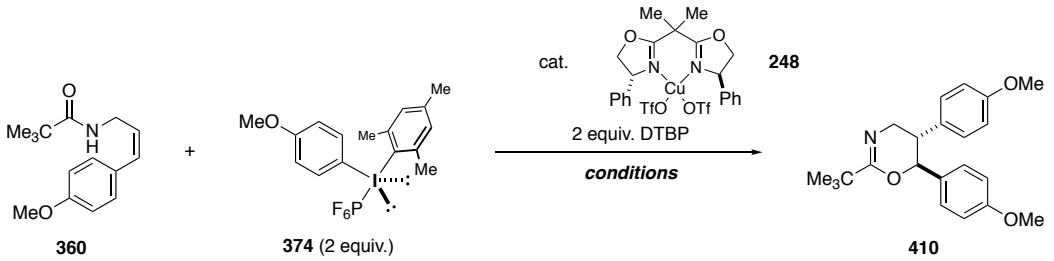
Efforts were first focused on improving the yield of the oxazine-formation reaction employing the *para*-methoxyphenyl substrate. The major problem to be addressed was that substantial quantities of alkene **413** were observed to be formed in the reaction, evidenced by time-course studies to result from oxazine decomposition (Scheme 80).



Scheme 80 – Generation of *E-*/*Z-* configured substituted allylic amide **413**

The effects of altering the time, catalyst concentration and temperature of the reaction were surveyed towards reducing levels of oxazine **410** decomposition (Table 20). Relative to the outcome with the original conditions (entry 1, 26% yield, 84% *e.e.*), a 7-hour reaction time furnished the oxazine product in a significantly improved yield (73%) but in reduced *e.e.* (75%). An intermediate 20-hour reaction period (entry 2) gave the product in 40% yield and 80% *e.e.*, both quantities between the values observed in the two previous studies. 5 mol% catalyst loading (entry 4) gave increased oxazine yield relative to the control reaction with 10 mol% copper, although still too low to be useful. Finally, a pronounced improvement was observed on lowering the reaction temperature to 40 °C, giving oxazine **410** in 79%

yield and 84% *e.e.* (entry 5). No further decrease in reaction temperature was explored owing to the slow rate of starting material conversion at 40 °C. Interestingly, both the trend of increased product enantioselectivity with prolonged reaction times (entries 1–3) and the observation of improved oxazine yields with reduced copper loading (entry 4) indicate a (diastereoselective) catalyst effect in degrading the product.



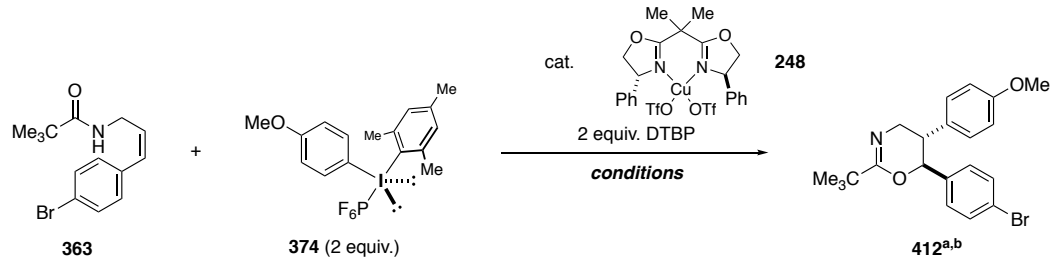
Entry	Conditions	Yield / %[a]	*e.e.* / %[b]
1	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 24 h	26	84
2	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 7 h	73	75
3	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 20 h	40	80
4[c]	5 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 24 h	48	n.d.
5	10 mol% **248**, CH_2Cl_2 (0.05 M), 40 °C, 30 h	**79**	**84**

[a] isolated yields; [b] *e.e.* determined by chiral HPLC assay; [c] yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate

Table 20 – Investigations towards increasing the yield of oxazine **360**

Attention was next turned to the reaction between *para*-bromophenyl substrate **363** and diaryliodonium salt **374**, previously observed to give good levels of oxazine formation only after prolonged reaction times (64% yield with 12% residual starting material after 43 hours). It was hoped that improved conversion to product could be obtained by increasing the catalyst loading, the iodonium salt loading, the reaction temperature or the reaction time (Table 21). Assessing two such modifications, further quantities of catalyst (entry 2) and iodonium salt (entry 3) were added to the reaction mixture after heating for 17 hours. Although these changes both gave increased product yield after a 24-hour period (relative to entry 1, control reaction), little further consumption of starting material was recorded after this time. Overall yields were lower than was observed for the initial test reaction in Table 19 (64%). Similarly, although increasing the temperature of the reaction to 60 °C (entry 4) provided a slight increase in NMR yield, starting material conversion remained moderate after a 24-hour period. Finally, increasing the catalyst loading to 15 mol% at the outset of the reaction gave greater oxazine yields than

were observed in earlier reactions (74% isolated) but provided low enantioselectivity (79% *e.e.*). The initial conditions (Table 19) remain the best compromise between reactivity and enantioselectivity.



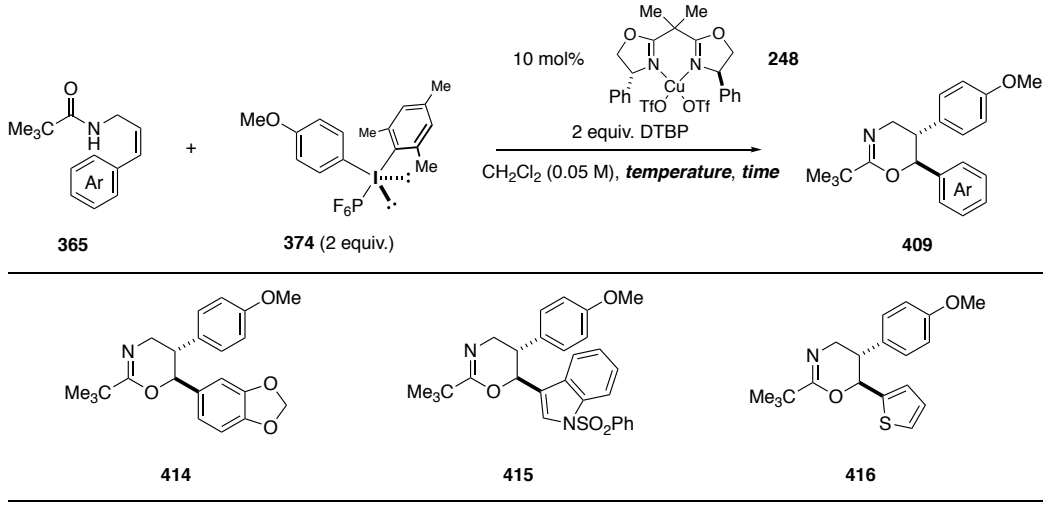
Entry	Conditions	Yield / %
1	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 24h	48 (40)
2	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 17 h *then*: 5 mol% **248** – 24 h	62 (32)
	48 h	51 (25)
3	10 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 17 h *then*: 1 equiv. **374** – 24 h	56 (43)
	48 h	53 (41)
4	10 mol% **248**, CH_2Cl_2 (0.05 M), 60 °C, 24 h	56 (37)
5[c]	15 mol% **248**, CH_2Cl_2 (0.05 M), 50 °C, 43 h	74 [79% *e.e.*]

[a] yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] bracketed quantity denotes residual starting material; [c] isolated yield, *e.e.* determined by chiral HPLC assay

Table 21 – Investigations into increasing the yield of oxazine **248**

Having determined that electron-donating substrates are tolerated under the *oxy*-arylation manifold, three further electron-rich allylic amides were tested and optimised (Table 22). Firstly, the use of dioxolane substrate **365** gave 73% isolated oxazine yield and 87% *e.e.* under the standard reaction conditions (entry 1). The reaction was then performed at 40 °C, in line with the improved formation of *bis*-*para*-methoxyphenyl oxazine **410** (entry 2). However, these reduced temperature conditions gave slow starting material conversion, ultimately furnishing the desired product in only 70% isolated yield after 46 hours and in an identical *e.e.* to the previous reaction. Lastly, the reaction time at 50 °C was shortened (entry 3), giving 80% product formation after 15 hours in a very good 89% *e.e.*. Next, exposing indole substrate **364** to the standard reaction conditions returned the desired oxazine product in 35% yield with no recovery of starting material (entry 4). As with the previous example, the reaction time was

reduced to three hours, giving the desired product in 62% NMR yield (entry 5). Finally, it was recorded that quenching the reaction after two hours furnished the oxazine product in 78% NMR yield, 62% isolated yield and in an excellent 91% *e.e.*. No product formation was detected on exposure of thiophenyl substrate **366** to reaction with iodonium salt **374**. Substantial thiophene decomposition was recorded, with 70% allylic amide lost within 15 minutes of heating.

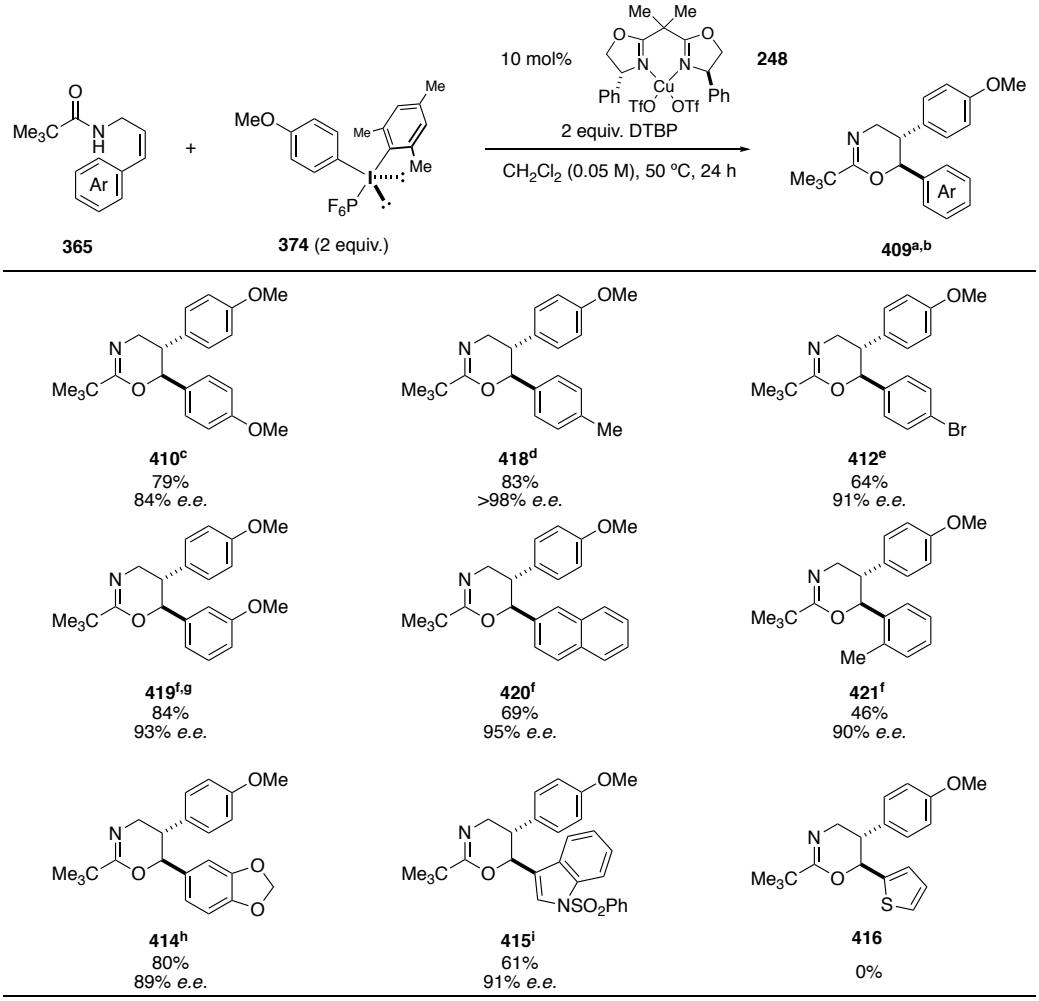


Entry	Product	Temperature/ T	Time / h	Yield / %[a]	*e.e.* / %[b]
1	**414**	50	20	73	87
2	**414**	40	46	70	87
3	**414**	50	15	**80**	**89**
4[c]	**415**	50	24	35	n.d.
5[c]	**415**	50	3	62	90
6[d]	**415**	50	2	**62**	**91**
7[c]	**416**	50	24	0	n/a
8[c]	**416**	50	2	0	n/a
9	**416**	50	0.25	0 (30)	n/a

[a] isolated yield; [b] *e.e.* determined by chiral HPLC assay; [c] 0.1 mmol scale, yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [d] 78% by NMR yield (1,2-dimethoxyethane as internal standard)

Table 22 – Scope investigations with electron-donating substrates

The scope of the substrate tolerance to the *oxy*-arylation reaction was compiled and further evaluated in collaboration with Elise Cahard and Dr Matthieu Tissot (Table 23). It was observed that a variety of aryl groups were tolerated as substituents on the allylic amide substrate to give oxazine products in 46–84% yield. The reaction appears to proceed faster for more electron-rich substrates (2 hours for **364**) and slower for more electron-poor allylic amides. The reduced reactivity with electron-deficient starting materials is evidenced by *para*-bromophenyl substrate **363** (σ 0.23) giving 12% recovered starting material after 43 hours and *meta*-methoxyphenyl substrate **417** (σ 0.12) requiring 15 mol% catalyst for good yields. Interestingly, *ortho*-substitution of the allylic amide aromatic ring is tolerated under the standard reaction conditions (**421**), though low yields (46%) are observed. No product was observed with the use of the thiophenyl substrate **366**. Levels of enantioselectivity are generally excellent, with slight reductions in *e.e.* observed with more electron-rich substrates.

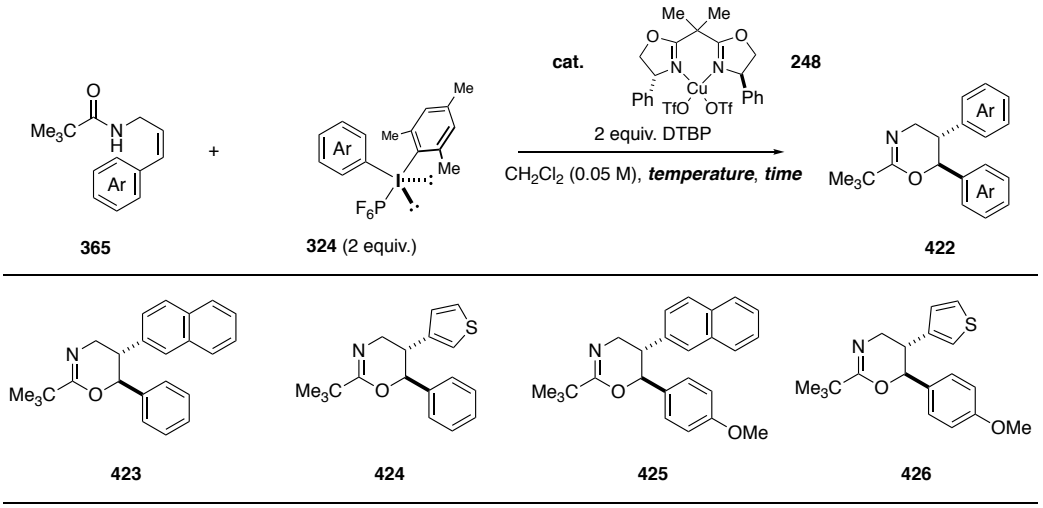


[a] isolated yield; [b] *e.e.* determined by chiral HPLC assay; [c] 40 °C, 30 h; [d] performed by Dr Elise Cahard; [e] 43 h, 12% residual starting material; [f] performed by Dr Matthieu Tissot; [g] 15 mol% **248**; [h] 15 h; [i] 2 h

Table 23 – Isolated substrate scope

2.7.3. Iodonium salt scope

Attention was next directed towards the iodonium salt scope of the enantioselective *oxy*-arylation reaction. As previous work has provided knowledge into the breadth of the iodonium salt tolerance to oxazine formation, studies were directed towards the challenging transfer of both 2-napthyl- and thiophenyl groups (Table 24, entries 1 and 2).[157] Exposure of the iodonium salts to the standard reaction conditions with simple phenyl substrate **315** furnished the desired compounds **423** and **424** in 36 and 32% isolated yield and 93 and 92% *e.e* respectively. These low yields can be attributed to low starting material conversions and could not be significantly improved by increasingly either catalyst loading or reaction time (entries 3–8). However, use of the more electron rich *para*-methoxyphenyl substrate with the same iodonium salts overcame the problem of low starting material conversion (entries 9 and 10) - both systems were observed to reach completion after 24 hours, giving moderate product yields of 42 and 55% respectively for oxazines **425** and **426**. Disappointingly, these products were formed in significantly lower enantioselectivity than is generally observed (52 and 63% *e.e.*). A mixture of diastereoisomers for oxazine **426** was also produced. Lastly, although slight improvements in yield and *e.e.* were observed with a 6-hour reaction time, enantioselectivity remained too low to be useful (entries 11 and 12).



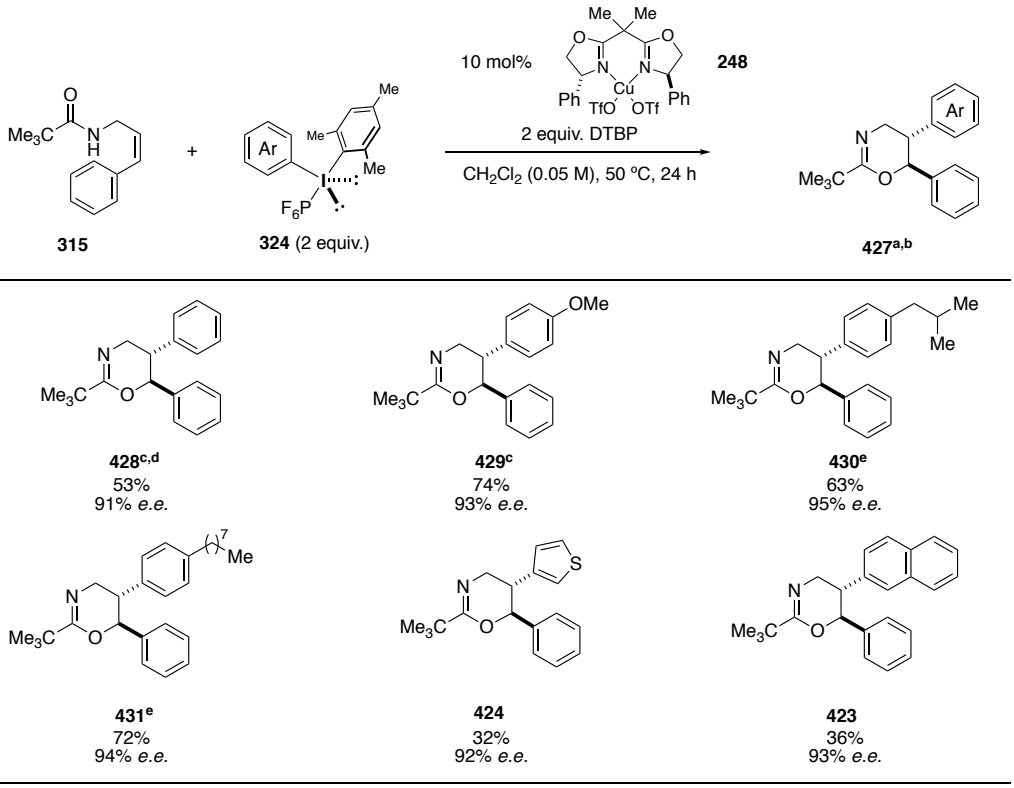
Entry	Product	Conditions	Yield / %[a,b]
1[c]	**423**	10 mol% **248**, 50 °C, 24 h	36 [93% *e.e.*]
2[c]	**424**	10 mol% **248**, 50 °C, 24 h	32 [92% *e.e.*]
3	**423**	10 mol% **248**, 50 °C, 24 h	41 (59)
		48 h	26 (59)
4	**423**	15 mol% **248**, 50 °C, 24 h	41 (58)

		48 h	29 (54)
5	**423**	20 mol% **248**, 50 °C, 24 h	42 (58)
		48 h	26 (57)
6	**424**	10 mol% **248**, 50 °C, 24 h	37 (58)
7	**424**	10 mol% **248**, 50 °C, 50 h	38 (55)
8	**424**	15 mol% **248**, 50 °C, 24 h	35 (63)
9[c]	**425**	10 mol% **248**, 50 °C, 24 h	42 [52% *e.e.*]
10[c]	**426**	10 mol% **248**, 50 °C, 24 h	55, 5:1 *d.r.* [63% *e.e.*]
11	**425**	10 mol% **248**, 50 °C, 6 h	60 [62% *e.e.*]
12	**426**	10 mol% **248**, 50 °C, 6 h	67, 4:1 *d.r.* [68% *e.e.*]

[a] yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate, bracketed quantity denotes residual starting material; [b] *e.e.* determined by chiral HPLC assay; [c] isolated yields

Table 24 – Investigations into increasing the transferral of under-reactive iodonium salts

The diaryliodonium salt scope of the reaction was also evaluated in collaboration with Elise Cahard and Dr Matthieu Tissot (Table 25). Synthetically useful to good oxazine yields (32–74%) and universally excellent levels of enantioselectivity (*e.e.* >90%) were observed with all the iodonium salts that were tested. Use of the phenyl-transferring iodonium salt **373** gave oxazine **428** together with achiral diphenyl enamide in an overall yield of 81%, in line with expectations for this electron-neutral iodonium salt. Complete oxazine selectivity and product yields in the range of 63–74% were observed with the use of *para*-alkylphenyl- and *para*-methoxyphenyl-substituted iodonium salts (**429–431**). As was previously described, the transfer of thiophenyl- and napthyl groups could be achieved to give oxazines **423** and **424** in low yields but with complete product selectivity and high *e.e.*.



[a] isolated yield; [b] *e.e.* determined by chiral HPLC assay; [c] performed by Elise Cahard; [d] 28% diphenyl enamide isolated [e] performed by Dr Matthieu Tissot

Table 25 – Isolated iodonium salt scope

Oxazine **428** gave high quality crystals suitable for X-ray analysis (Figure 8). These data allowed for the determination of the absolute configuration of this product as the (*S*,*S*)-enantiomer and allowed configurational assignment of the remainder of the oxazine products by analogy. Interestingly, when compared with the crystal structure of enamide **399** (Figure 7, page 63), it was noted that the two allylic amide arylation products appear to arise from reaction on opposite faces of the alkene.

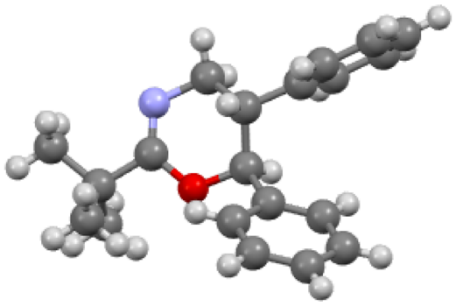
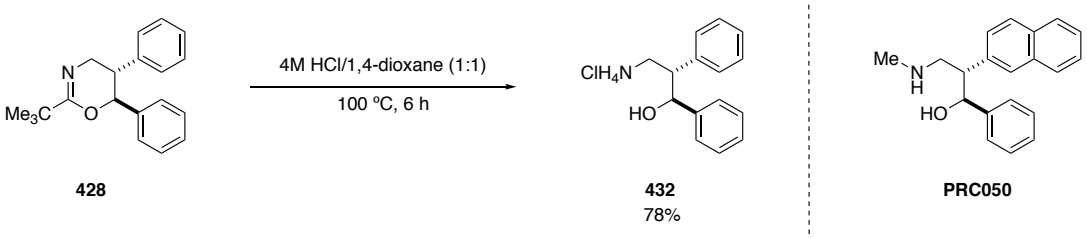


Figure 8 – X-ray crystal structure of enamide **428** – Elise Cahard

2.8 Applications

Attention was turned towards the application of our enantioselective and regiodivergent allylic amide arylation to the production of molecules useful to the wider chemical community. In line with such an aim, Elise Cahard has previously determined that oxazine products can be cleaved to amino-alcohol salts (Scheme 81).[157] This hydrolysis reaction will now allow enantioselective access to compounds such as the anti-depressant PRC050.[163]



Scheme 81 – Hydrolysis of oxazine **428** to amino-alcohol **432**,[157] application to the synthesis of PRC050

Similarly, it was considered that hydrolysis of the enamide products would give β,β'-diaryl aldehydes (Figure 9a). This class of molecule comprises the backbone of a number of pharmaceutically important compounds such as the antimuscarinic tolteridine (**434**) and the monoamine transporter inhibitor indatraline **435** (Figure 9b).[164] It was envisaged that there would be industrial interest in the formation of these aldehydes by a novel enantioselective means.

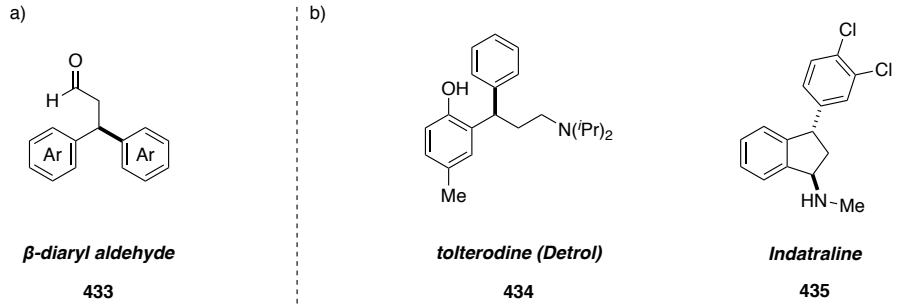
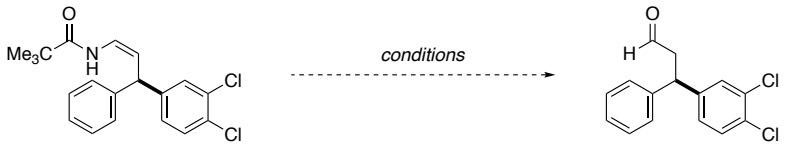


Figure 9 – a) β-diaryl aldehyde; b) pharmaceutical agents derived from β-diarylaldehydes

Eleven conditions were studied for the hydrolysis of enamide **389** (Table 26), chosen for these investigations as the aldehyde product is an intermediate in Aggarwal's synthesis of indatraline.[165–168] Biphasic conditions of mild aqueous acid and dichloromethane were initially tested as the enamide hydrolysis medium, allowing production of the desired aldehyde in moderate yields only after prolonged heating (entries 1 and 2). The poor mass balance observed in the reactions was attributed to hydrate formation in the aqueous phase, precluding extraction into the organic medium. Anhydrous acidic conditions were therefore next tested (entries 3 and 4), disappointingly giving enamide decomposition and apparent polymerisation. Attention was then turned to monophasic acidic conditions with the use of concentrated aqueous hydrochloric acid in 1,4-dioxane (entries 5 and 6). Relative to heating at 50 °C

for 14 hours, improved product yields were attained at room-temperature with stirring for 90 minutes (62 *vs.* 44%) although no further improvement in yield was achieved by quenching the reaction with aqueous sodium hydroxide (entry 7). Pleasingly, improved product yields were observed on reducing the concentrations of the reaction (entries 9 and 10, 75 and 79% yield), although further dilution (entry 11) gave poorer conversion. Finally, tetrahydrofuran was employed as the reaction solvent to improve miscibility (entry 12). Excellent conversion to product was observed, allowing aldehyde production in a 92% yield following work-up with solid sodium carbonate and drying over anhydrous sodium sulfate.



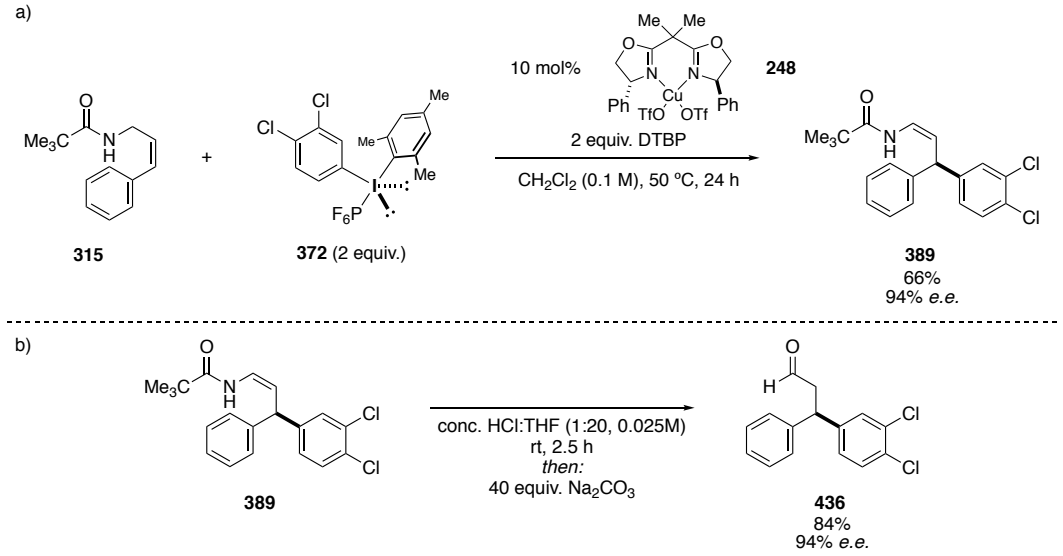
389 **436**

Entry	Conditions	Work-up[a]	Yield / %[b]
1	3M HCl (aq.):CH_2Cl_2 (1:1, 0.025 M), 60 °C, 24 h	**A**	50
2[c]	3M HCl (aq.):CH_2Cl_2 (1:1, 0.025 M), 60 °C, 27 h	**A**	58
3	1.1 equiv. TfOH, CH_2Cl_2 (0.1 M), rt, 2 h	**A**	0[d]
	50 °C, 24 h	**A**	0
4	4 M HCl in 1,4-dioxane (0.05 M), rt, 2 h;	**A**	0[e]
5	Conc. HCl:1,4-dioxane (1:5, 0.04 M), 50 °C, 14 h	**A**	44
6	Conc. HCl:1,4-dioxane (1:5, 0.04 M), rt, 1.5 h	**A**	62
7	Conc. HCl:1,4-dioxane (1:5, 0.04 M), rt, 4 h	**B**	58
8	Conc. HCl:1,4-dioxane (1:10, 0.05 M), rt, 0.5 h	**B**	75
9	Conc. HCl:1,4-dioxane (1:20, 0.025 M), rt, 4 h	**B**	79
10	Conc. HCl:1,4-dioxane (1:50, 0.01 M), rt, 4 h	**B**	74
11	Conc. HCl:THF (1:20, 0.025 M), rt, 4 h	**C**	**92**

[a] **A**: quench with sat. aq. $NaHCO_3$, extract with CH_2Cl_2; dry over $MgSO_4$ and concentrate; **B**: quench with 10% aqueous NaOH, extract with CH_2Cl_2, dry over $MgSO_4$ and concentrate; **C**: addition solid Na_2CO_3, filter solution through Na_2SO_4 and concentrate: [b] yield determined following work-up by ^1H NMR using 1,2-dimethoxyethane; [c] isolated yield; [d] 100% conversion to *trans*-enamide; [e] polymerisation suspected

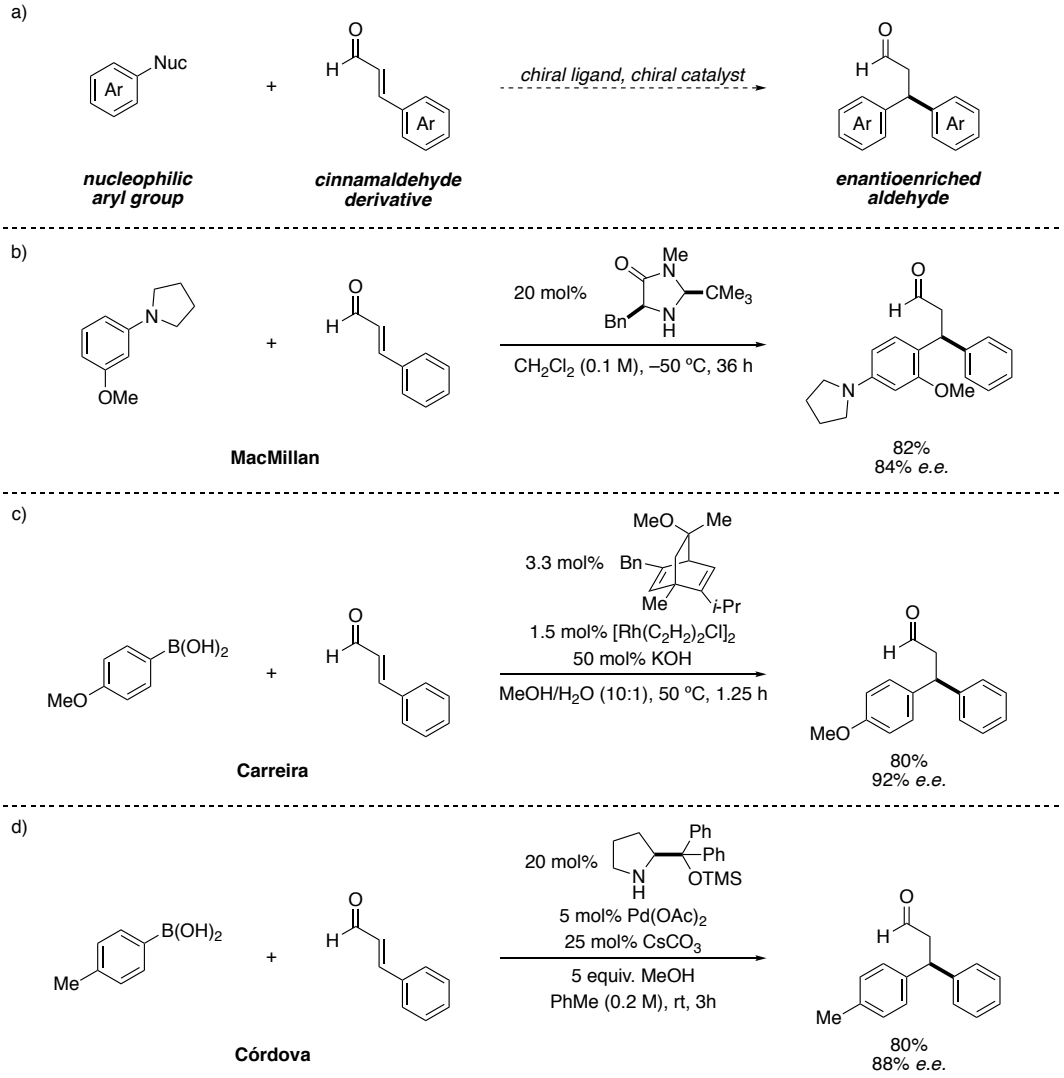
Table 26 – Optimisation of the enamide hydrolysis procedure

With conditions for the hydrolysis of enamide products in hand, enantioenriched enamide **389** was freshly prepared and converted into aldehyde **436** in a good overall yield (Scheme 82).



Scheme 82 – a) enantioselective generation of enamide **389**; b) enamide hydrolysis to furnish the desired highly enantioenriched β-diaryl aldehyde **436**

All enantioselective methods for the generation of β-diarylaldehydes reported to date have proceeded *via* the addition of a nucleophilic aryl group to some cinnamaldehyde derivative (Scheme 83a). Three types of reaction based on this strategy have been developed: organocatalysed (Scheme 83b),[169] metal-catalysed (Scheme 83c)[170–172] and synergistically catalysed (Scheme 83d).[173] Compared with these formal conjugate addition reactions, the generation of enantioenriched aldehydes *via* the production of enamides represents a polarity-reversed process. Rather than employing a nucleophilic aryl group and an electrophilic alkene equivalent, our copper-catalysed process employs an electrophilic aryl group (iodonium salt) and a nucleophilic alkene (allylic amide). It is envisaged that this umpolung strategy will provide a useful orthogonal method for the synthesis of challenging β-diarylaldehydes.

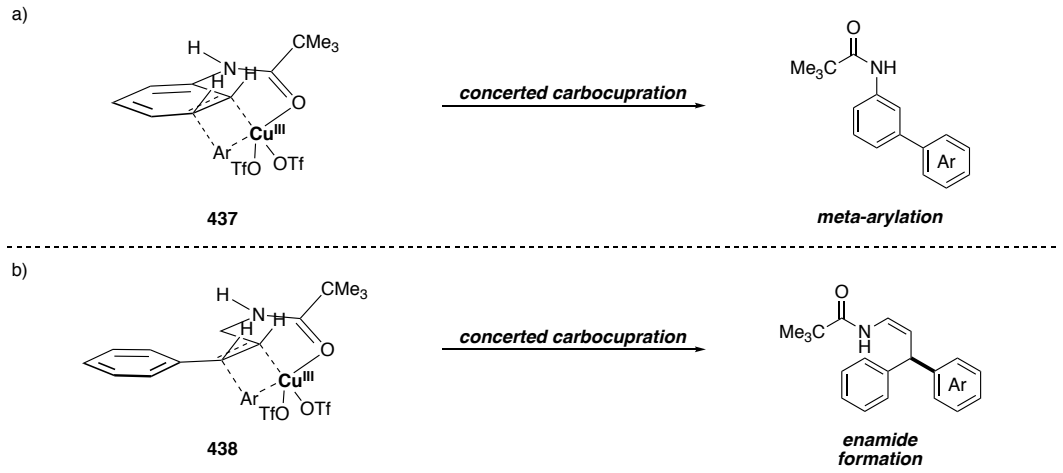


Scheme 83 – a) simplified reaction overview; b) MacMillan's organocatalysed addition of anilines to cinnamaldehydes;[169] c) Carreira's rhodium-catalysed addition of boronic acids to cinnamaldehydes;[170] d) Cordova's synergistic palladium-catalysed addition of boronic acids to *in situ* generated iminum species.[173]

2.9 Mechanistic Rationale

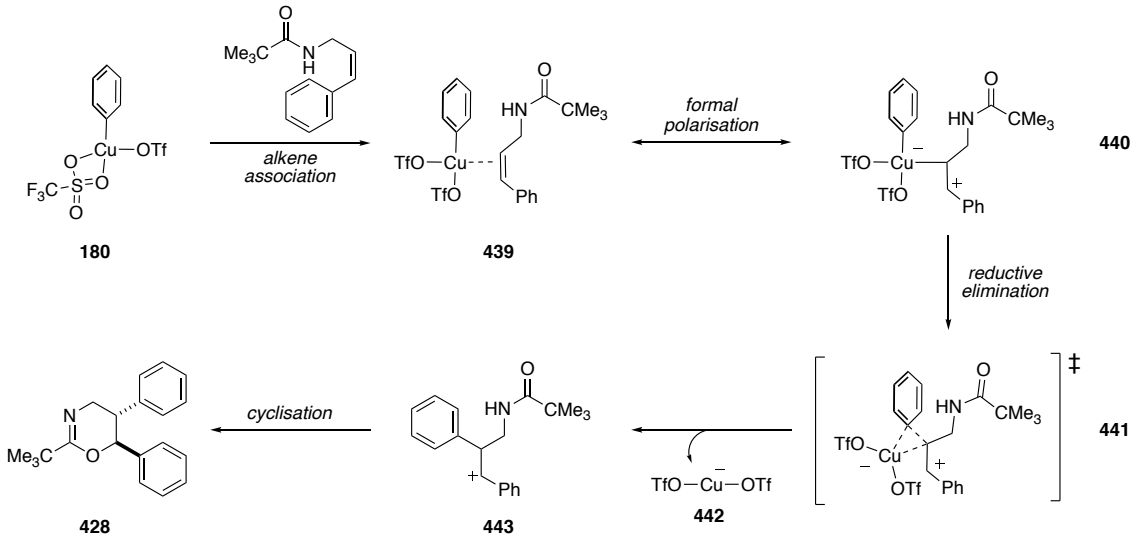
The system under investigation appears to lie at a point of mechanistic cross-over with one pathway leading to enamide formation and the other to oxazine generation. Tentatively, it is proposed that these two products result from two different alkene functionalisation modes.

A carbonyl-directed carbocupration process (**437**) has been evidenced in Li and Wu's computational evaluation of Gaunt's *meta*-arylation procedure (Scheme 84a).[126,129] It is proposed that an analogous functionalisation mode (**438**) may occur with allylic amide substrates to give enamide formation (Scheme 84b). Such a concerted carbocupration process could be rationalised to be favoured with the use of electron-deficient diaryliodonium salts as the putative aryl-copper(III) intermediate will be relatively more electrophilic, driving association of the carbonyl moiety.



Scheme 84 – a) computed concerted carbocupration to give *meta*-arylation;[129] b) proposed concerted carbocupration to give enamide formation

Conversely, oxazine formation might occur *via* benzylic carbocation **443**, generated through reductive elimination-like transition state **441** from a highly-polarised alkene-copper(III) complex (Scheme 85). Mono-dentate alkene co-ordination may be expected to be favoured under the reaction conditions employing electron-rich iodonium salts. The relatively increased electron density on the copper(III) centre would preclude carbonyl-binding, thereby disfavouring enamide formation.



Scheme 85 – proposed oxazine-formation pathway proceeding though a reductive elimination-like process to give carbocation **443**

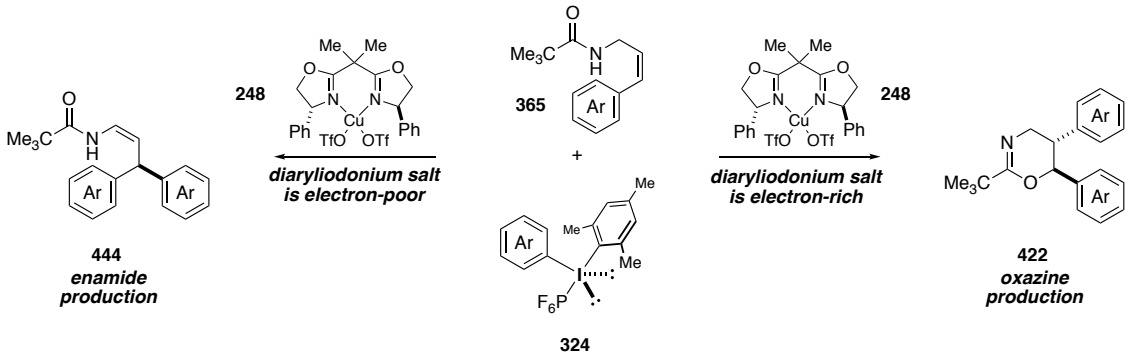
Computational evidence for both carbocupration and reductive elimination-like alkene functionalisation processes are provided in chapter 4 of this thesis.

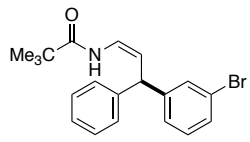
2.10 Summary

This chapter has described the development of a novel copper-catalysed enantioselective and regiodivergent process for the functionalisation of alkenes with diaryliodonium salts. A range of allylic amides were shown to react with diaryliodonium hexafluorophosphates to furnish diaryl oxazines and enamides in high enantioselectivity. The regioselectivity of the arylation process was demonstrated to be dependent on the electronic nature of the transferred aryl group, with electron-rich iodonium salts giving oxazine products and electron-poor salts giving enamides. The products are shown to have applications in pharmaceutical development, with it demonstrated that enamide products may be hydrolysed to enantioenriched β-diaryl aldehydes.

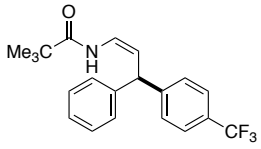
A full reaction scope is given on the following pages (Tables 27 and 28). Compounds synthesised personally are marked 'HPJM' whilst compounds synthesised by my collaborators Elise Cahard and Dr Matthieu Tissot are marked 'EC' and 'MT' respectively.

The work described in this chapter was published in the Journal of the American Chemical Society.[174]

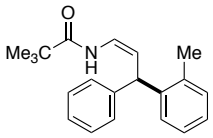




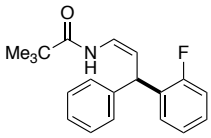
332 (HPJM)
55%
95% *e.e.*



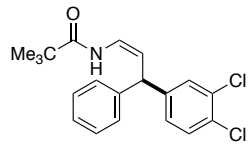
383 (HPJM)
70%
91% *e.e.*



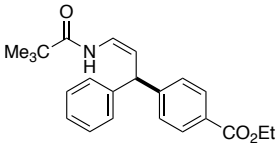
384 (HPJM)
40%
97% *e.e.*



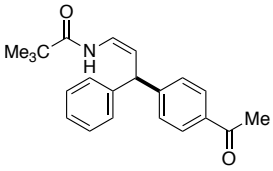
385 (HPJM)
42%
>98% *e.e.*



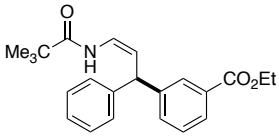
389 (HPJM)
58%
93% *e.e.*



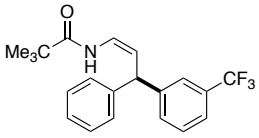
390 (EC)
55%
93% *e.e.*



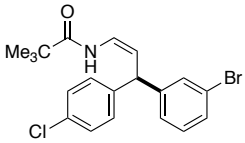
391 (EC)
42%
82% *e.e.*



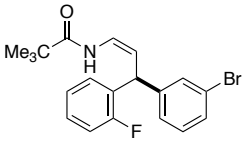
392 (EC)
52%
92% *e.e*



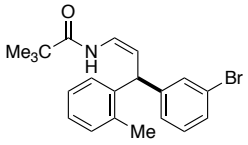
393 (EC)
60%
94% *e.e.*



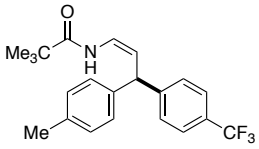
378 (HPJM)
42%
93% *e.e.*



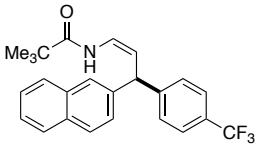
379 (HPJM)
12%
89% *e.e.*



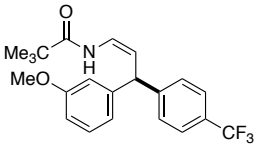
380 (HPJM)
34%
97% *e.e.*



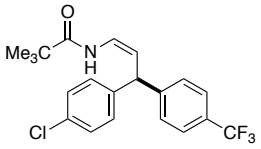
395 (EC)
74%
96% *e.e.*



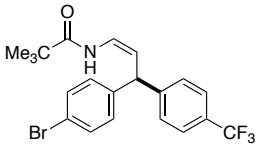
396 (HPJM)
52%
95% *e.e.*



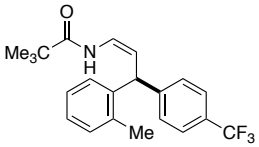
397 (EC)
69%
90% *e.e.*



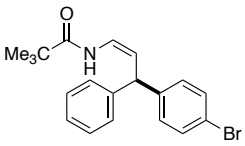
398 (HPJM)
34%
92% *e.e.*



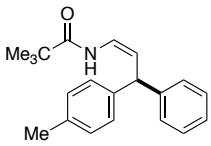
399 (HPJM)
28%
89% *e.e.*



403 (HPJM)
26%
>98% *e.e.*

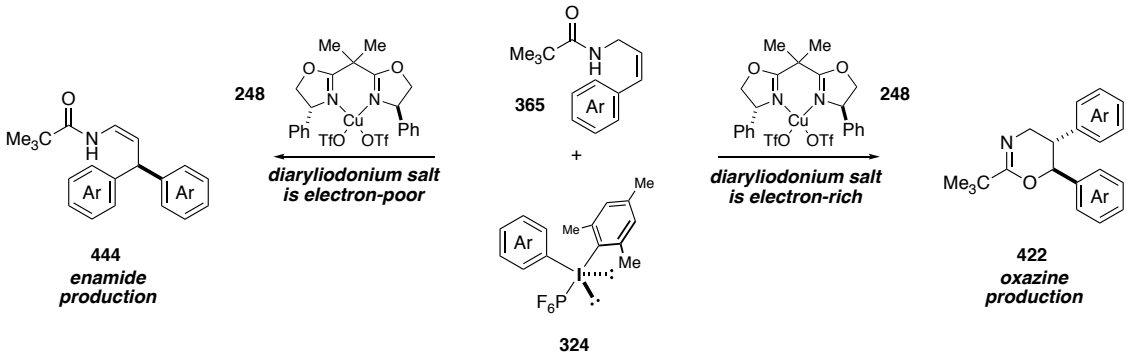


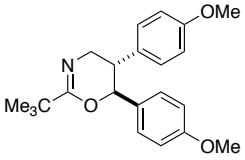
405 (EC)
50%
94% *e.e.*



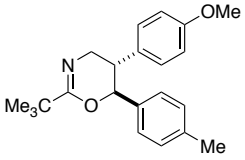
407 (MT)
26%
97% *e.e.*

Table 27 – Full and attributed enamide scope of the enantioselective and regiodivergent alkene arylation procedure employing allylic amides and diaryliodonium salts

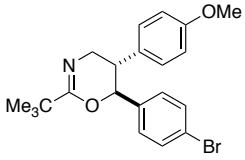




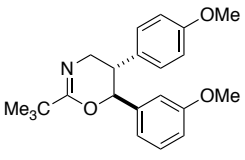
410 (HPJM)
79%
84% *e.e.*



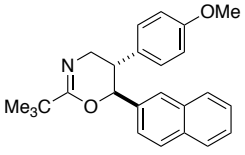
418 (EC)
83%
>98% *e.e.*



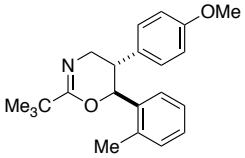
412 (HPJM)
64%
91% *e.e.*



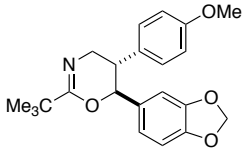
419 (MT)
84%
93% *e.e.*



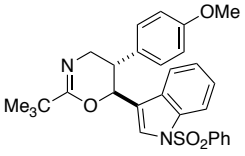
420 (MT)
69%
95% *e.e.*



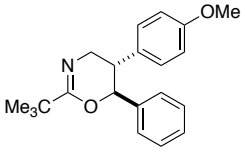
421 (MT)
46%
90% *e.e.*



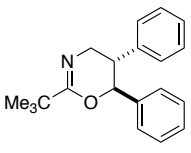
414 (HPJM)
80%
89% *e.e.*



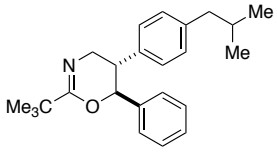
415 (HPJM)
61%
91% *e.e.*



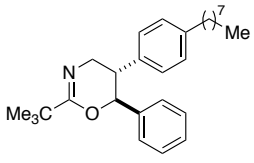
429 (EC)
74%
93% *e.e.*



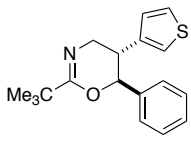
428 (EC)
53%
91% *e.e.*



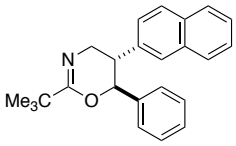
430 (MT)
63%
95% *e.e.*



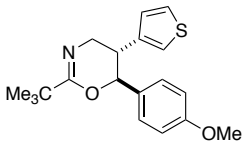
431 (MT)
72%
94% *e.e.*



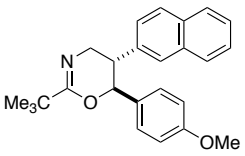
424 (HPJM)
32%
92% *e.e.*



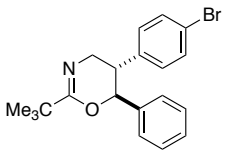
423 (HPJM)
36%
93% *e.e.*



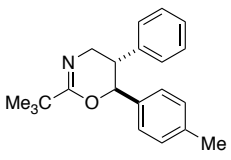
426 (HPJM)
67% (4:1 *d.r.*)
68% *e.e.*



425 (HPJM)
60%
62% *e.e.*



406 (EC)
36%
89% *e.e.*



407 (MT)
29%
98% *e.e.*

Table 28 – Full and attributed oxazine scope of the enantioselective and regiodivergent alkene arylation procedure employing allylic amides and diaryliodonium salts

3 Studies Towards the Total Synthesis of (−)-Lyngbyaloside B

3.1 Project Overview

This chapter describes efforts towards the total synthesis of the polyketide natural product (−)-lyngbyaloside B. Our strategy was based on the use of a copper-catalysed *oxy*-alkenylation as the key disconnection, unifying an elaborate homoallylic carbamate and a complex alkenyl iodonium salt. Work was carried out towards fragment synthesis and coupling studies.

3.2 (−)-Lyngbyaloside B

3.2.1. Isolation and structure determination

In 2002 Moore and Paul reported the isolation of a polyketide derived from the Palauan cyanobacterium *Lyngbya sp*.[175] This compound was determined to display structural similarity to the previously-reported homologues lyngbyaloside **445** and lyngbouilloside **446** and was accordingly named (−)-lyngbyaloside B.[176,177] Following extensive NMR analysis, the stereochemical structure of the macrolidal natural product was tentatively assigned as **447** (Figure 10).

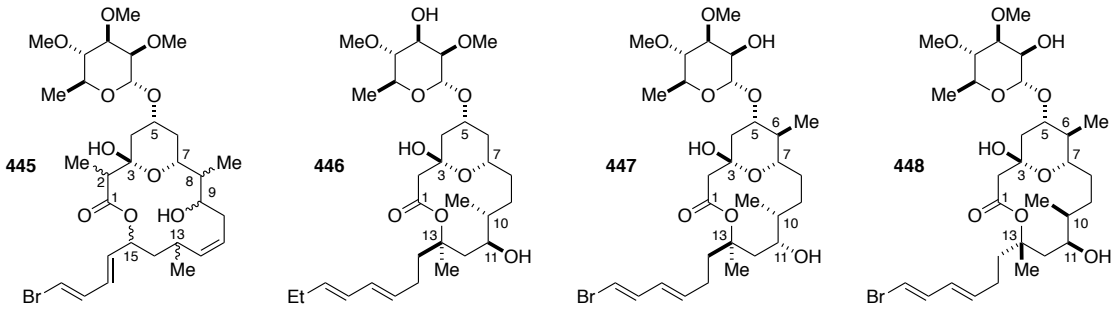


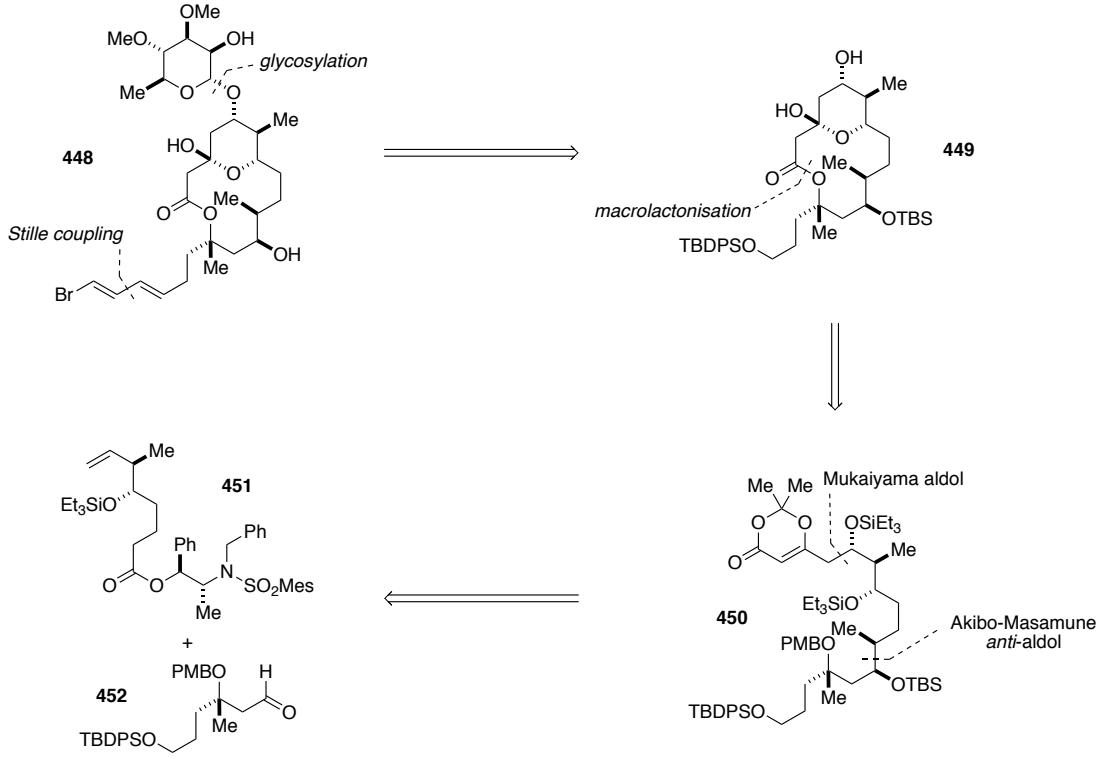
Figure 10 – Members of the lyngbyaloside family (proposed, partial and confirmed structures)[175–178]

Interested in both the backbone structure and the reported cytotoxicity of (−)-lyngbyaloside B, the Fuwa group chose to independently synthesise the described compound. However, following the generation of **447**, they found the characterisation data to not match those of the Moore and Pauls' isolated material.[178] A similar result was observed following efforts by the groups of Cossy, Ley and Hansen towards the synthesis of the known aglycone of Lyngbouilloside.[179–181]

Comparing the NMR data of the isolated and synthesised (−)-lyngbyaloside B, Fuwa noted that the greatest degree of stereochemical disagreement lay in the C-9–13 region of the polyketide backbone. Extensive computational conformational analysis was performed on candidate isomers with this backbone portion altered. It was concluded from these studies that the (10*S*,11*S*,13*S*)-isomer **448** would most closely fit the observed spectroscopic data. The new stereochemical assignment was confirmed in Fuwa's 2015 synthesis of **448**.[178,182]

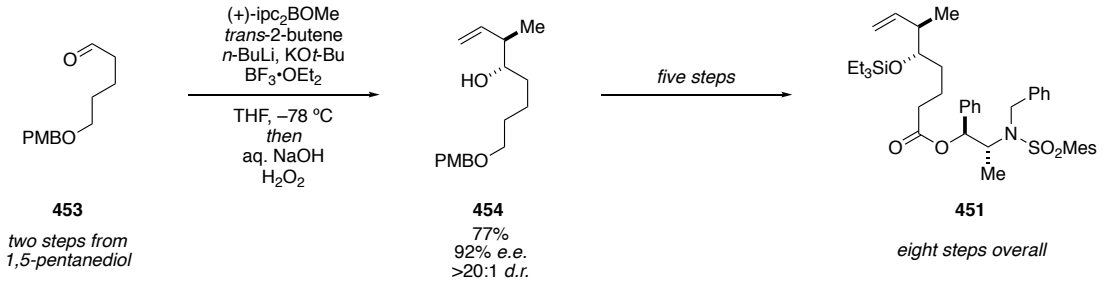
3.2.2. Reported total synthesis

Fuwa's 2015 synthesis remains the only total synthesis of (–)-lyngbyaloside B reported in the literature. The retrosynthetic approach for this target initially focused on the formation of aglycone **449** by disconnecting the peripheral groups by Stille coupling and glycosylation. The simplified structure was accessed from linear precursor **450** *via* an acyl-ketene macrolactonisation. Following some simple oxidative manipulations on a pendant alkene, the introduction of the dioxinone handle was achieved through a vinylogous Mukaiyama aldol reaction. It was determined that the advanced polyketide backbone could be constructed with an Abiko-Masamune *anti*-aldol from the relatively simple fragments **451** and **452** (Scheme 86).



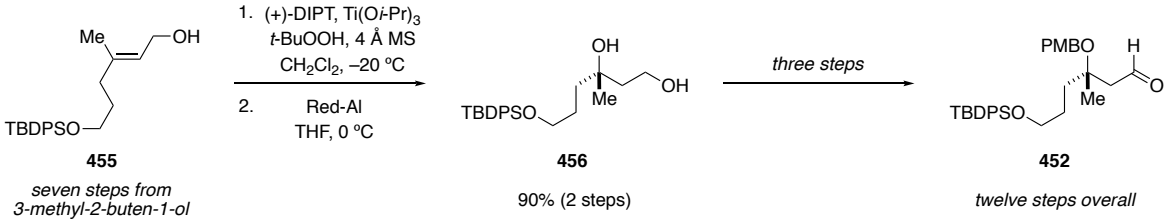
Scheme 86 –Fuwa's retrosynthetic strategy to access (–)-lyngbyaloside B[182]

Abiko-Masamune ester **451** can be accessed in eight steps from commercial starting materials (Scheme 87). The key step in this synthesis is the installation of the desired C-6 and C-7 stereochemistry through a Brown crotylation with known aldehyde **453**.[183] Following generation of crotylated compound **454**, the desired fragment **451** was produced in five steps through high-yielding protecting group manipulations, oxidation chemistry and an auxiliary coupling.



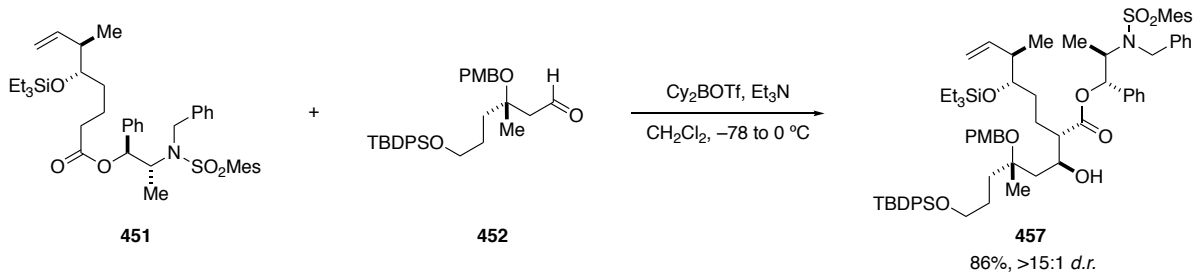
Scheme 87 –Fuwa's synthesis of Akibo-Masamune ester **451**[182]

The aldehyde coupling partner **452** was accessed in twelve steps from commercial materials (Scheme 88). Following simple synthetic manipulations, a Sharpless asymmetric epoxidation of allylic alcohol **455**, followed by regioselective reductive epoxide opening, gave key enantiopure diol **456** in excellent yield and set the stereochemistry of the C-13 position of (–)-lyngbyaloside B. With diol **456** in hand, a two-step PMB protection of the tertiary alcohol group and a Parakh-Doering oxidation furnished the desired aldehyde fragment.



Scheme 88 –Fuwa's synthesis of aldehyde coupling partner **452**[182]

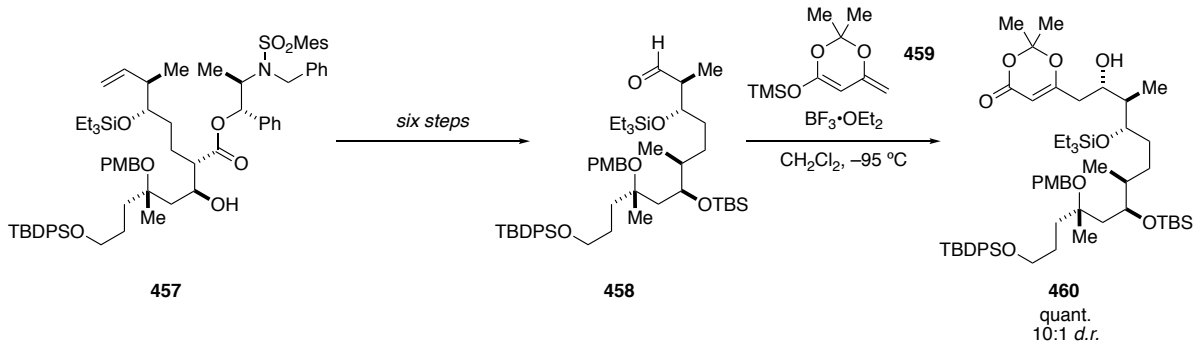
The fragments were joined by a diastereoselective Abiko-Masamune *anti*-aldol reaction to give the desired aldol adduct **457** in 86% yield and to fix the C-10 and C-11 stereocentres of the target compound (Scheme 89).[184]



Scheme 89 –Abiko-Masamune aldol reaction furnishing **457**[182]

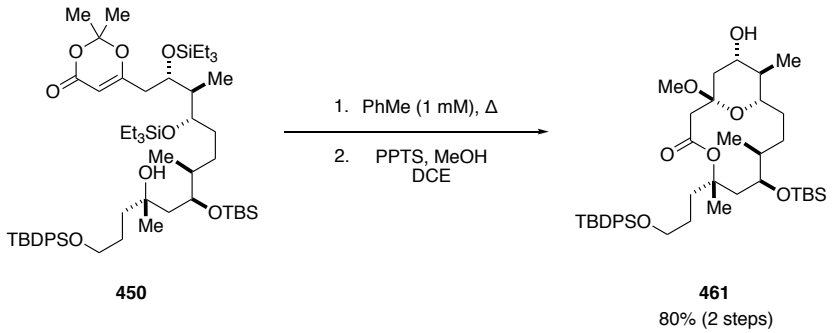
Aldol product **457** was converted to advanced aldehyde **458** in a six-step reaction sequence involving silyl protection of the secondary alcohol, reduction of the ester moiety, alkene dihydroxylation and oxidative diol cleavage. However, following the generation of the aldehyde, a vinylogous Mukaiyama

aldol reaction between **458** and enol ether **459** easily furnished the dioxinone-bearing linear precursor **460** in quantitative yield and in good diastereoselectivity (Scheme 90).



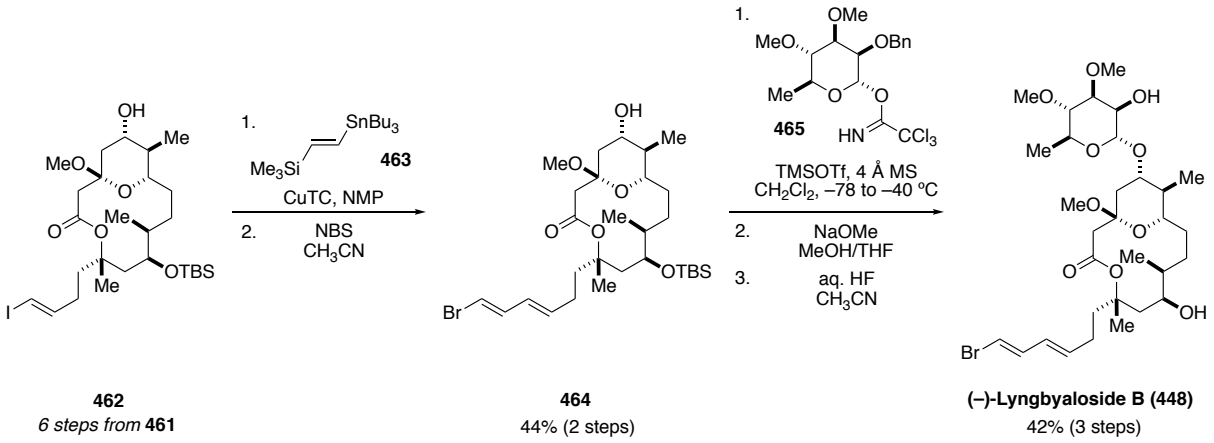
Scheme 90 –Manipulations to furnish linear precursor **460**[182]

Following simple protecting-group manipulations to give intermediate tertiary alcohol **450**, the compound underwent an acyl-ketene macrolactonisation on heating in toluene. Direct treatment of the crude lactone with mild acid in methanol furnished the protected aglycone in 80% yield over two steps (Scheme 91).



Scheme 91 –Macrolactonisation of tertiary alcohol **450** to furnish aglycon **461**[182]

Transformation of aglycone **461** into vinyl iodide **462** required a laborious six-step reaction sequence involving deprotection, oxidation, alkynylation, hydrostannylation and iodination processes. However, with the vinyl iodide in hand, modified Stille coupling with stannane **463** and subsequent treatment with NBS cleanly furnished dienyl-bromide **464**. This late-stage intermediate was glycosylated then the hydroxyl-protecting groups removed to finally furnish (–)-lyngbyaloside B **448** (Scheme 92).

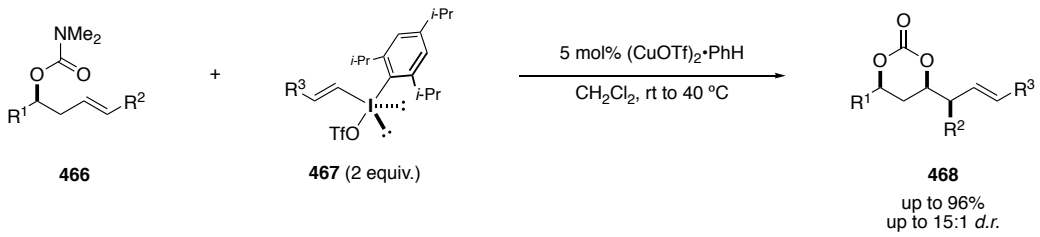


Scheme 92 –Stille coupling and glycosylation end-game to give (–)-Lyngbyaloside B **448**[182]

Whilst Fuwa's 32-step synthesis effectively generates the target molecule, inefficiencies are apparent in the production of both the polyketide backbone (22 steps to **460**) and the pendant dienyl bromide moiety. We believed that there was scope to improve this synthesis with the use of more contemporary synthetic methods.

3.3 Retrosynthetic Strategy

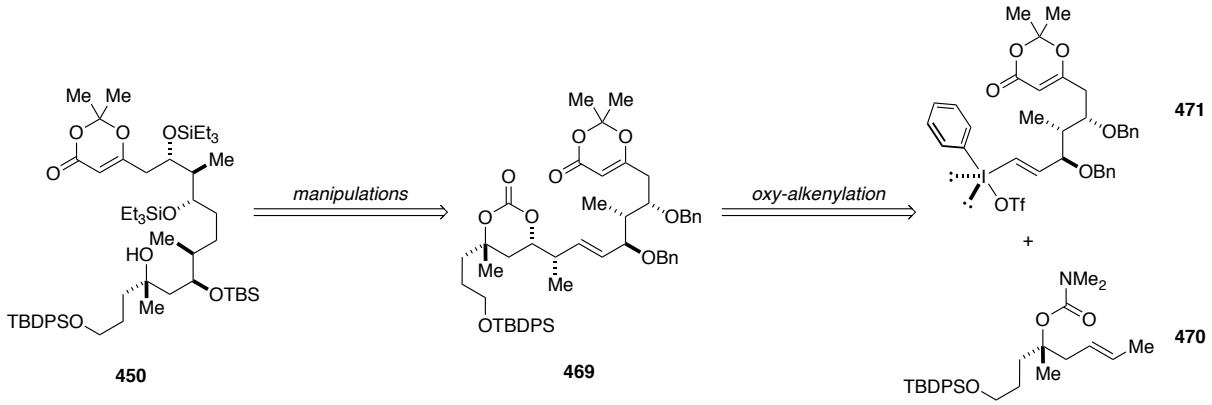
The Gaunt group has recently developed a diastereoselective copper-catalysed *oxy*-alkenylation reaction employing homoallylic carbamates and alkenyl(aryl)iodonium salts (Scheme 93).[158] The resulting homoallylic carbonates represent masked 1,3-*syn*-diols, a common substitution pattern observed in polyketides. It was questioned whether this alkene functionalisation process could be used in natural product synthesis, particularly as a fragment coupling method.



Scheme 93 –Gaunt's copper-catalysed *oxy*-alkenylation procedure towards homoallylic carbonates **468**[158]

(–)-Lyngbyaloside B was chosen as a target for the complex fragment unification strategy as it contains an all-*syn* relationship in the C-10–13 region of the molecule and an adjacent fully saturated C_2 unit. It was recognised that a formal synthesis of the target compound could be achieved by converting homoallylic carbonate **469** to dioxinone **450**, an advanced intermediate in Fuwa's total synthesis. The carbonate would be produced from the coupling of highly functionalised carbamate southern fragment **470** with complex iodonium salt northern fragment **471** (Scheme 94). The unification of these

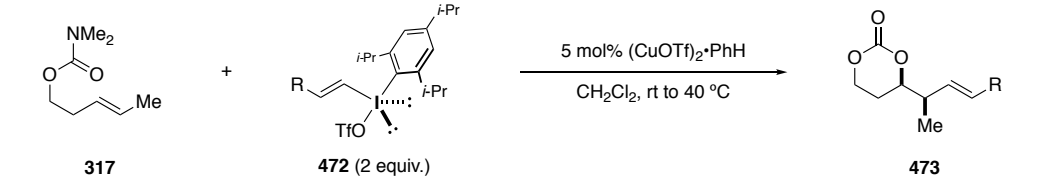
components would test not only the application of our C–C bond-forming methodology, but also the accessibility and utility of functionality-rich iodonium salts.



Scheme 94 – Proposed retrosynthesis from intermediate **450**

3.4 Model System Studies

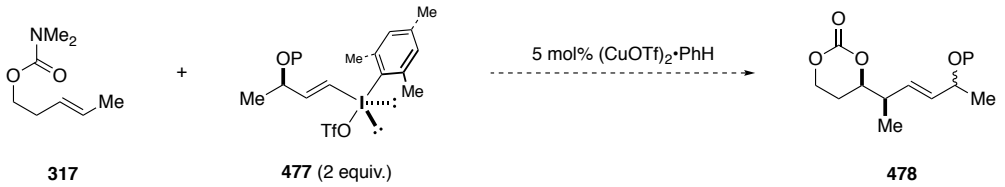
Gaunt's copper-catalysed homoallylic carbamate alkenylation methodology tolerates the use of a variety of iodonium salts. Within the reported scope of the reaction, the generation of three carbonate examples are particularly relevant to the formation of (–)-lyngbyaloside B – allylic disubstituted carbonate **474** and allylic oxygenated compounds **475** and **476** (Table 29).[158]



474	**475**	**476**
96%	78%	41%
15:1 *d.r.*	15:1 *d.r.*	10:1 *d.r.*

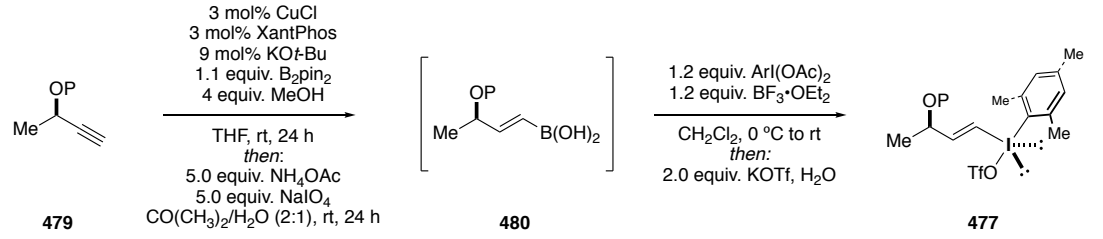
Table 29 – Relevant substitution tolerance of the alkenyl iodonium salt **472** to Gaunt's *oxy*-alkenylation[158]

The above examples provide evidence that the desired complex fragment coupling will be tolerated under copper-catalysed *oxy*-alkenylation conditions. However, no examples are shown for the transfer of iodonium salts bearing a more relevant secondary allylic ether motif. Initial efforts were therefore directed towards the investigation of a model reaction between homoallylic carbamate **317** and some more representative iodonium salt (**477**) (Scheme 95).



Scheme 95 – Model fragment coupling to give a homoallylic carbonate with a secondary allylic ether motif

A three-step procedure was identified for the production of iodonium salts bearing the desired allylic substitution. The reaction sequence employs a copper-catalysed alkyne borylation,[185] a boronic ester hydrolysis and a Lewis-acid promoted iodonium salt formation. Three alkenyl(aryl)iodonium salts were synthesised by this method (Table 30) in order to assess the effect of both the oxygen protecting group and the steric bulk of the iodonium salt aryl group on the outcome of the model *oxy*-alkenylation reaction.



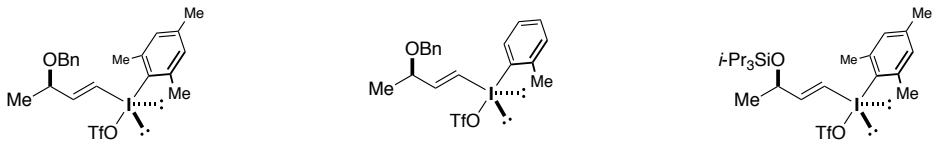
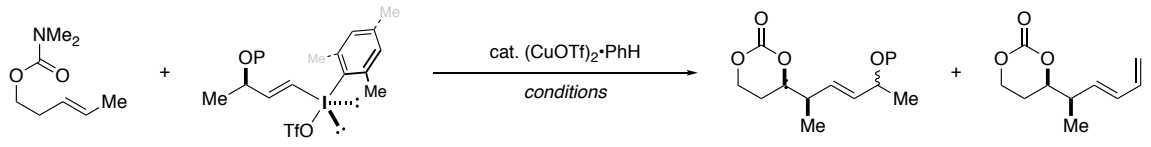


Table 30 – Production of model iodonium salts **481**, **482** and **483**

The coupling of the new iodonium salts with model homoallylic carbamate substrate **317** was then tested (Table 31). Investigations began by employing the original coupling conditions reported by our group,[158] giving moderate to good starting material conversions but little desired product formation (<8% yield in all cases, entries 1–3). Diene **484** was observed to be the major product of all the reactions (19–13% yield), implying either the iodonium salts or the products to be unstable with respect to a deleterious elimination of the protected allylic alcohol.



317 **477** (2 equiv.) **478** **484**

Entry	Iodonium Salt	Conditions	Yield / %[a]		
			478[b]	**484**[c]	**317**
1	**481**	10 mol% [Cu], CH_2Cl_2 (0.025 M), rt, 18 h	<8	19	22
2	**483**	10 mol% [Cu], CH_2Cl_2 (0.025 M), rt, 18 h	<5	15	53
3	**482**	10 mol% [Cu], CH_2Cl_2 (0.025 M), rt, 18 h	<7	13	13
4	**481**	10 mol% [Cu], CH_2Cl_2 (0.025 M), 0 °C, 24 h	23	0	77
5	**481**	10 mol% [Cu], CH_2Cl_2 (0.1 M), 0 °C, 24 h	33	0	63
6	**481**	10 mol% [Cu], CH_2Cl_2 (0.05 M), 0 °C, 24 h	33	0	54
		44 h	29	tr	44
		64 h	27	8	37
7	**481**	10 mol% [Cu], CH_2Cl_2 (0.05 M), −15 °C, 24 h	0	0	70
8	**481**	10 mol% [Cu], CH_2Cl_2 (0.05 M), 10 °C, 24 h	20	tr	29
9	**481**	10 mol% [Cu], CH_2Cl_2 (0.05 M), 0 °C, 24 h	33	0	43
		+10mol% [Cu], 42 h	29	tr	39
10	**483**	10 mol% [Cu], CH_2Cl_2 (0.05 M), 0 °C, 24 h	<5	0	66
11	**482**	10 mol% [Cu], CH_2Cl_2 (0.05 M), 0 °C, 24 h	**46**	0	47

[a] yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] yield quoted as the sum of four possible diastereoisomers; [c] yield quoted as the sum of two possible diastereoisomers

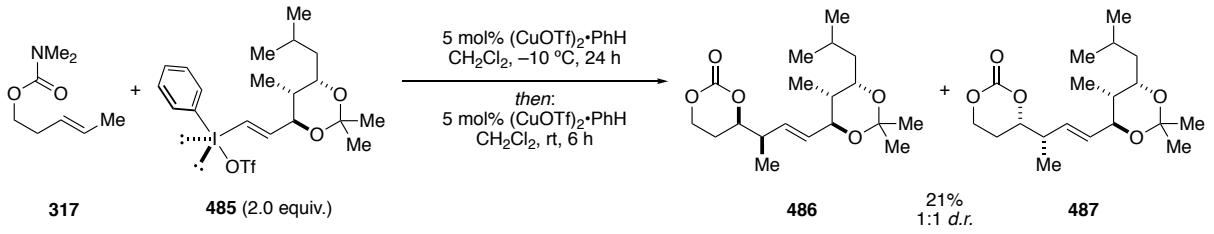
Table 31 − Investigations into the viability of the model coupling between homoallylic carbamate **317** and iodonium salts **481**, **482** and **483**

Work was directed towards disfavouring the elimination process (Table 31, entries 4–9). It was discovered that lowering the temperature of the reaction employing iodonium salt **481** to 0 °C precluded

formation of the diene and gave increased product yields (23%) despite reduced levels of starting material conversion (entry 4). Similarly, increasing the concentration of the reaction at 0 °C (entry 5, 0.05 M) provided an improved 33% homoallylic carbonate yield, although no further increase in yield was observed at 0.1 M (entry 6). Extending the reaction time from 24 to 44 and 64 hours resulted in significant starting material decomposition and no further product formation. Finally, no improvement in carbonate yield was obtained by further varying the reaction temperature (−15 °C for entry 7 and +10 °C for entry 8) or by increasing the loading of the catalyst in the reaction (entry 9).

It was hoped that changing either the oxygen protecting group or the non-transferring aryl group of the iodonium salt would lead to increased *oxy*-alkenylation yields. As such, the conditions giving the best reactivity with benzyl-protected alkenyl(mesityl)iodonium salt **481** (0.05 M, 0 °C, 10 mol% Cu) were applied to coupling reactions employing TIPS-protected and *ortho*-tolyl-bearing iodonium salts **483** and **482** (Table 31, entries 10 and 11). Although only trace product was observed with the allylic hydroxyl group being protected as a tri-*iso*-propylsilyl ether, the use of the less sterically-encumbered benzyl-protected iodonium salt furnished the coupled product in 46% yield. This result demonstrates that iodonium salts bearing secondary allylic ether motifs will react with homoallylic carbamates to give the corresponding carbonate in useful yields, thereby evidencing the viability of the proposed complex fragment coupling. Further, reducing the sterics of the iodonium salt appears to improve conversion.

My colleague Dean Holt extended the model coupling studies to the use of acetonide-protected iodonium salt **485**, designed to bear the relative stereochemistry and oxygenation pattern of the C-5,6,7 portion of (–)-lyngbyaloside B (Scheme 96).[186] Although no reaction with homoallylic carbamate **317** was detected after 24 hours at −10 °C, carbonates **486** and **487** were obtained in 21% combined yield after a further six hours of reaction time at room-temperature and with an additional portion of catalyst. The observed 1:1 diastereoselectivity was expected given the achiral nature of the homoallylic carbonate substrate. Despite the low yields, the production of carbonate products **486** and **487** proves that polyoxygenated and stereochemically-rich alkenyl(aryl)iodonium salts can be tolerated in our copper-catalyed *oxy*-alkenylation reaction. This result provides crucial evidence for the likely tolerance of our desired complex iodonium salt **471** under the same reaction manifold.



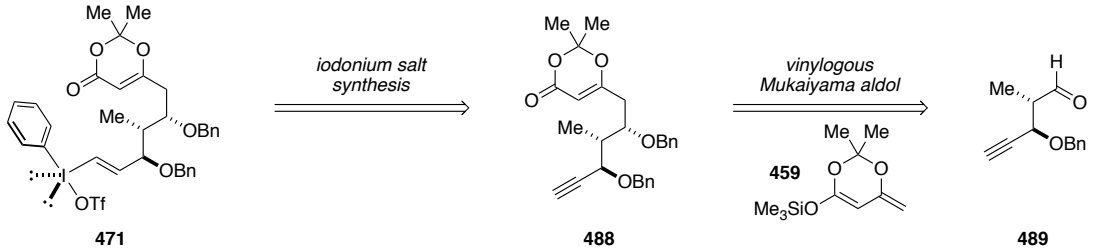
Scheme 96 – Model coupling between model substrate **317** and iodonium salt **485** – Dean Holt[186]

Efforts were next directed towards the synthesis of the key synthetic fragments. Dean Holt turned his attention towards the synthesis of homallylic carbamate **470**, later investigated by Dominik Reich. The following work focuses on the synthesis of complex iodonium salt **471**.

3.5 First Generation Synthetic Strategy

3.5.1. Synthetic strategy

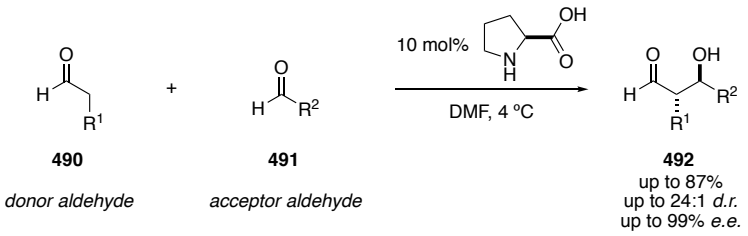
It was planned to generate iodonium salt **471** from parent alkyne **488** using the previously-described borylation, oxidative pinacol ester cleavage and iodonium salt formation sequence (see Table 30 above). The intermediate alkyne was to be accessed in two steps from aldehyde **489** by a diastereoselective Mukaiyama aldol reaction with dioxionone nucleophile **459** followed by benzyl protection of the resulting hydroxyl group (Scheme 97). Attention was therefore first turned to the production of **489.**



Scheme 97 –Retrosynthetic strategy to iodonium salt **471** from key aldehyde intermediate **489**

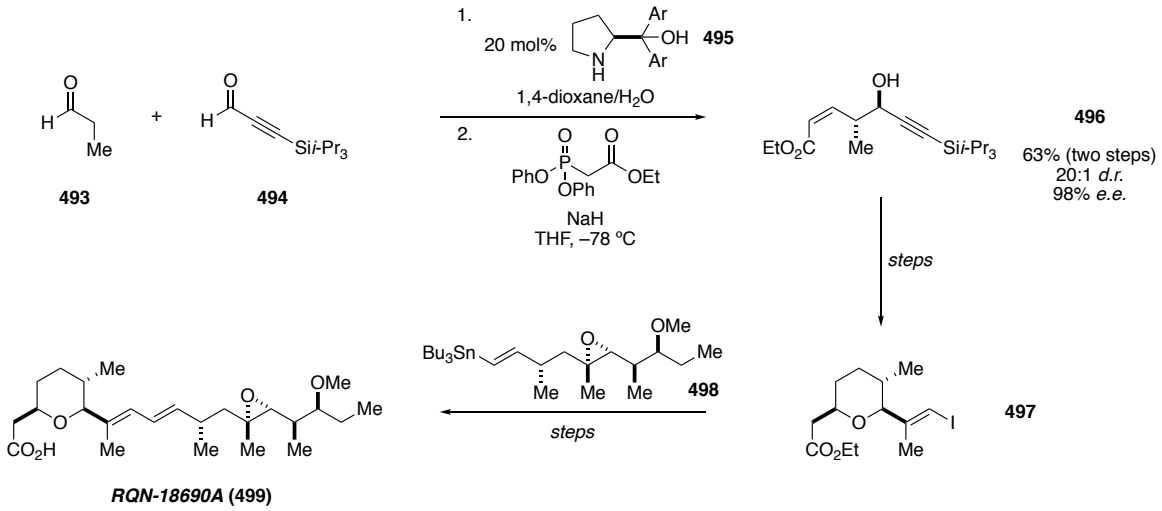
3.5.2. Generation of aldehyde 489

In 2002, MacMillan described an enantioselective cross-aldol procedure using simple aldehydes as substrates and proline as a catalyst (Scheme 98).[187] No pre-functionalisation of the reagents is required as the reaction is controlled by the donor and acceptor nature of the two different aldehyde components.



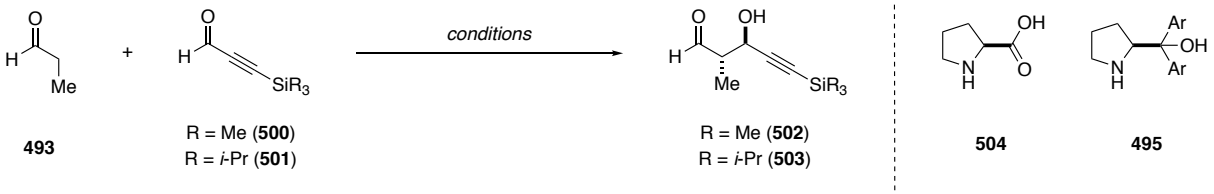
Scheme 98 – MacMillan's proline-catalysed cross-aldol[187]

Matsumoto and Hayashi modified MacMillan's organocatalytic chemistry for their synthesis of RQN-18690A (**499**) (Scheme 99).[188,189] In their studies, prolinol **495** was employed to catalyse an aldol union between **493** and **494**. The resulting product then underwent an *in situ* Ando reaction to give enyne **496** in high *e.e.* and *d.r.*. Subsequent synthetic manipulations gave tetrahydropyran western fragment **497**, directly consumed in a Stille coupling with eastern fragment **498** to furnish the protected target.



Scheme 99 – Matsumoto and Hayashi's synthesis of RQN-18690A **499**; Ar = 3,5-$(CF_3)_2$-Ph[189]

The above catalytic and enantioselective aldol reactions would provide a concise route towards target aldehyde **489**. The coupling of propionaldehyde to propargylic aldehydes **500** and **501** was therefore tested using both MacMillan's proline- and Hayashi's prolinol-catalysed cross-aldol reactions (Table 32). However, despite significant efforts, it was disappointing to note that no desired product was observed with the use of MacMillan's cross-aldol process (entries 1 and 2). Similarly, although Matsumoto and Hayashi's conditions gave the observation of product formation (entry 3, 80% NMR yield, 10:1 *d.r.*), the resulting aldol adduct could not be isolated and decomposed with all efforts to protect the sensitive hydroxyl group. The instability of the product aldehyde explains why Matsumoto and Hayashi perform an Ando coupling without intermediate isolation. Such a strategy is not viable in our synthesis as the aldehyde functionality is required for the later Mukaiyama aldol reaction.



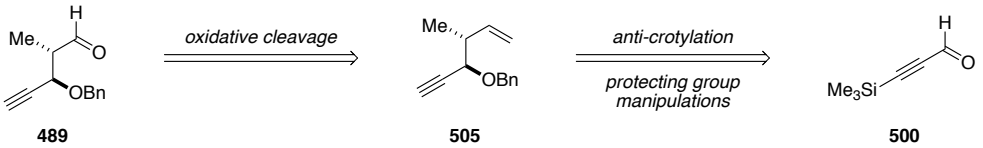
Entry	Aldehyde	Conditions	Yield / %[a]
1[187]	**500**	2.0 equiv. **493**, 10 mol% **504** DMF, 4 °C, 20 h	0
2[187]	**501**	2.0 equiv. **493**, 10 mol% **504** DMF, 4 °C, 20 h	0

3[189]	**501**	1.5 equiv. **493**, 20 mol% **495**[b]	80 (10:1 *d.r.*)
		1,4-dioxane/H_2O (19:1), rt, 4 h	unstable to isolation

[a] yields determined by ^1H NMR using 1,3,5-trimethoxybenzenetricarboxylate; [b] Ar = 3,5-$(CF_3)_2$-Ph

Table 32 – Efforts towards the generation of aldehydes **502** and **503** by organocatalytic aldol processes

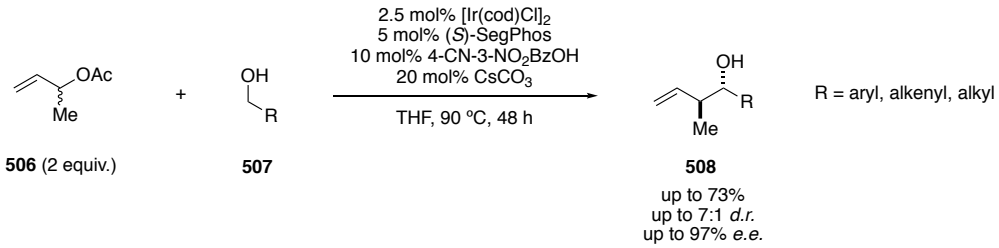
Alternative methods were sought for the enantioselective generation of the desired 1,2-*anti* configured aldehyde **489**. Attention was turned towards the use of an *anti*-crotylation and alkene oxidation strategy (Scheme 100).



489 **505** **500**

Scheme 100 – Crotylation/oxidation strategy towards aldehyde **489**

Krische has recently reported a versatile *anti*-diastereoselective iridium-catalysed transfer hydrogenation crotylation procedure, employed to generate a wide range of crotylated adducts from the combination of crotyl acetate (**506**) and primary alcohols (Scheme 101).[190] This methodology, together with a milder procedure employing pre-formed iridium catalyst **513**,[191] was tested for the crotylation of propargylic alcohols **509** and **510** (Table 33). Disappointingly, no desired product formation was detected in any reaction. It was concluded that the Krische methodologies will not tolerate these propargylic alcohols as substrate, possibly due to catalyst poisoning.



506 (2 equiv.) **507** **508**

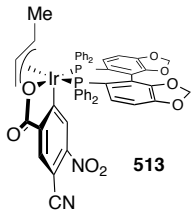
up to 73%
up to 7:1 *d.r.*
up to 97% *e.e.*

Scheme 101 – Krische's iridium-catalysed transfer-hydrogenation crotylation procedure[190]

506 (2 equiv.)

R = Me (**509**)
R = *i*-Pr (**510**)

R = Me (**511**)
R = *i*-Pr (**512**)

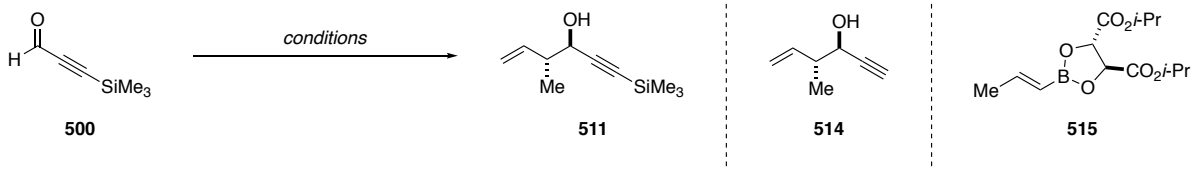


513

Entry	Alcohol	Conditions	Yield / %
1[190]	**509**	2.5 mol% $[Ir(cod)Cl]_2$, 5 mol% (*R*)-SegPhos 10 mol% 4-CN-3-NO_2BzOH, 20 mol% $CsCO_3$ THF, 90 °C, 48 h	0
2[190]	**510**	2.5 mol% $[Ir(cod)Cl]_2$, 5 mol% (*R*)-SegPhos 10 mol% 4-CN-3-NO_2BzOH, 20 mol% $CsCO_3$ THF, 90 °C, 48 h	0
3[191]	**509**	5 mol% **513**, 50 mol% K_3PO_4, 5 equiv. H_2O THF, 60 °C, 48 h	0
4[191]	**510**	5 mol% **513**, 50 mol% K_3PO_4, 5 equiv. H_2O THF, 60 °C, 48 h	0

Table 33 – Attempts to generate crotylated species **511** and **512** using Krische's methodologies

Efforts were next directed towards the crotylation of propargyl aldehyde **500** using stoichiometric boron reagents (Table 34). Brown crotylation (entry 1), using an *in situ*-formed di-*iso*-pinocamphenylborane reagent, gave low yields of the desired product and only moderate levels of diastereoselectivity but provided very good levels of *e.e.*.[192] The low yield can be attributed to the desilylation of **511** to alcohol **514**, observed to form an azeotrope with the reaction solvent. Disappointingly, efforts to collect this product by distillation were unsuccessful. Gratifyingly, use of Roush's crotylation method (entry 2) gave the desired product **511** in 86% yield, excellent diastereoselectivity and good enantioselectivity.[193] The lack of product desilylation is attributed to the milder work-up conditions required with the di-*iso*-propyl tartrate boronic ester. Although crotyl alcohol **511** has been reported previously, there is disagreement in the literature regarding the sign of the optical rotation.[192,194] Mosher ester analysis was therefore carried out, confirming the product to be the desired *R,R*-isomer and supporting Hall's configurational assignment.[194] 7.6 g of crotyl alcohol **511** was produced for further studies using Roush's method.

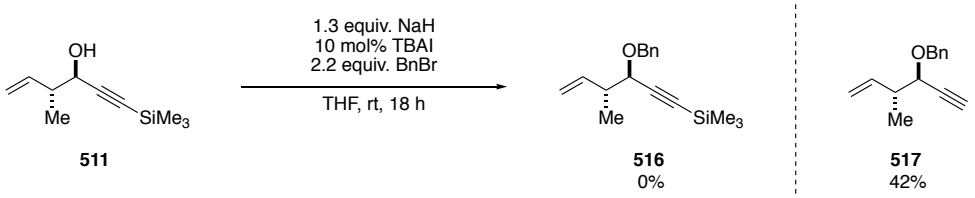


500 **511** **514** **515**

Entry	Conditions	Result
1[192] 17.5 mmol	excess *trans*-butene, 2.0 equiv. KO*t*-Bu, 2.0 *n*-BuLi	
	2.0 equiv. MeOB((+)-*i*pc)$_2$, THF, −78 °C to −40 °C to −78 °C, 30 min	15% yield
	then: 1.0 equiv. **500**, 2.0 equiv. BF_3•OEt_2, THF, −78 °C, 2 h	11:1 *d.r.*
	then: MeOH, −78 °C to rt	88% *e.e.*
	then: $NaBO_3$•$(H_2O)_4$, THF/H_2O (2:1), 18 h, 18 h	
2[193] 48.7 mmol	1.0 equiv. **500**, 1.2 equiv. **515**	86% yield
	4 Å MS, PhMe, −78 °C	>20:1 *d.r.*
	then: NaOH (2M aq.), −78 °C to rt	75% *e.e.*

Table 34 – Crotylation of aldehyde **500** with stoichiometric boron reagents

Attention was then focused on the benzyl-protection of secondary alcohol **511**, first attempted with Garcia's propargylic alcohol benzylation conditions using sodium hydride, benzyl bromide and catalytic tetrabutylammonium iodide (Scheme 102).[195] Interestingly, no product **516** was formed from this reaction, with it instead observed that desilylated ene-yne-ol **517** was produced in 42% yield. As the synthetic plan ultimately requires the removal of the terminal silyl group, this result was not considered disadvantageous. However, the overall yield of the transformation was clearly too low to be synthetically useful and required optimisation.

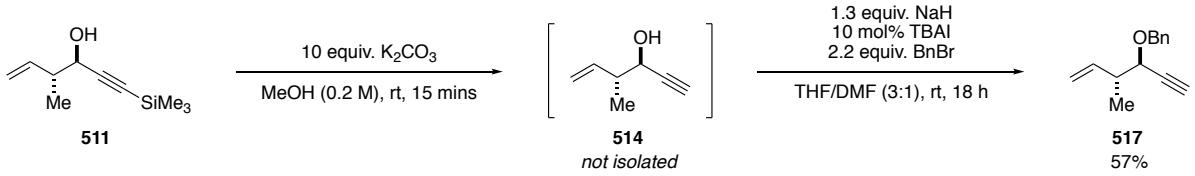


511 **516** 0% **517** 42%

Scheme 102 – Attempted direct benzylation of enyne **511**

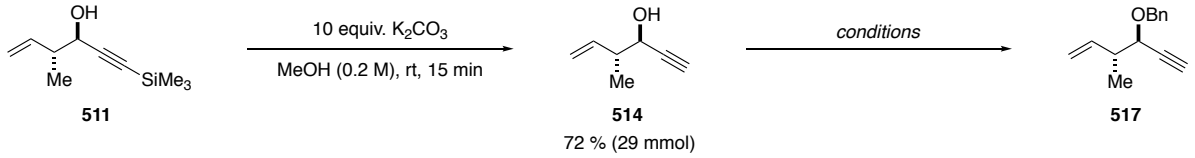
The limited yields of the above reaction were attributed to the transfer of the trimethylsilyl groups from the alkynes to the *in situ*-generated *oxy*-anions, blocking oxygen benzylation and leading to starting material decomposition. As such, a two-step procedure to first desilylate the alkyne and then benzylate

the alcohol was tested. Though this benzylation strategy gave a superior yield to the previous experiment, it was still lower than was desired (Scheme 103).



Scheme 103 – Two-step deprotection/protection of **511** to give **517** (3 mmol scale)

Both the volatility of intermediate alcohol **514** and the removal of the excess benzyl bromide from the crude product mixture were considered to be the major causes of the low yield of the benzylation process. Efforts were therefore directed towards the isolation the intermediate alcohol and the use of reaction conditions employing reduced equivalents of benzylating reagent (Table 35). Pleasingly, volatile alcohol **514** could be isolated in 72% yield on a large scale by careful kugelrohr distillation. A subsequent benzylation reaction employing 1.4 equivalents of benzyl bromide and using sodium hydride as a base gave 71% yield of the desired product (entry 1). However, although both yields in this reaction sequence are good, the two-step yield was reduced relative to the previous conditions. Pleasingly, it was observed that use of sodium hydroxide (entry 2) gave significantly improved product yields (87%, 63% over two steps). Up to 2.4 g of benzyl ether **517** was synthesised in a single batch using this latter method.

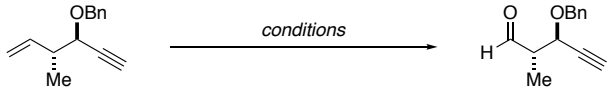


Entry	**Conditions**	**Yield / %[a]**
1[196]	1.2 equiv. NaH, 10 mol% TBAI, 1.4 equiv. BnBr	71
5 mmol	THF, rt, 18 h	(51% over two steps)
2[197]	1.3 equiv. BnBr, 5 mol% TBAI, 4 equiv. NaOH	87
5 mmol	H_2O, rt, 18 h	(63% over two steps)

Table 35 – Assay of benzylation conditions employed reduced equivalents of benzyl bromide

A two-operation dihydroxylation/oxidative cleavage method was chosen to transform alkene **517** into the desired aldehyde. Using Curran's reported method, the alkene substrate was dihydroxylated with catalytic osmium tetroxide and one equivalent of NMO. *Meta*-periodic acid was added to the reaction mixture after 16 hours to oxidatively cleave the crude diol,[192] initially giving a poor (41%) product yield and high levels of stereochemical erosion (3:1 *d.r.*) (Table 36, entry 1). On repeating the reaction, it was

observed that improved yields and reduced C-2 epimerisation could be achieved by concentrating the crude aldehyde at 0 °C following work-up (52% yield, 7:1 *d.r.*, entry 2). Likewise, use of periodic acid rather than *meta*-periodic acid (entry 3) led to further improvements in both yield and *d.r.* (71%, 9:1, entry 3). Finally, it was discovered that a two-step procedure employing silica-supported sodium *meta*-periodate allowed the production of the desired aldehyde in very good yields and with minimal loss of stereochemical integrity (80%, >20:1 *d.r.*, entry 4).[198] The configurationally-unstable aldehyde **518** was directly consumed following production.



517
>20:1 *d.r.*

518

Entry	Conditions	Work-up	Result[a]
1[192]	1.5 mol% OsO_4, 1 equiv. NMO Me_2CO/H_2O (8:1), rt, 16 h *then*: 1.5 equiv. HIO_4, 0 °C, 0.5 h	$Na_2S_2O_3$ (sat. aq.) EtOAc extract concentrate at rt	41% (3:1 *d.r.*)
2	1.5 mol% OsO_4, 1 equiv. NMO Me_2CO/H_2O (8:1), 0 °C to rt, 16 h *then*: 1.5 equiv. HIO_4, 0 °C, 0.5 h	$Na_2S_2O_3$ (sat. aq.) EtOAc extract concentrate at 0 °C	52% (7:1 *d.r.*)
3	1.5 mol% OsO_4, 1 equiv. NMO Me_2CO/H_2O (8:1), 0 °C to rt, 16 h *then*: 1.5 equiv. H_5IO_6, 0 °C, 0.5 h	$Na_2S_2O_3$ (sat. aq.) EtOAc extract concentrate at 0 °C	71% (9:1 *d.r.*)
4[198]	1. 0.4 mol% OsO_4, 4 equiv. NMO THF/H_2O (4:3), rt, 168 h 2. $NaIO_4$•SiO_2, CH_2Cl_2[b]	$Na_2S_2O_3$ (sat. aq.) EtOAc extract concentrate at 0 °C	80% (>20:1 *d.r.)*

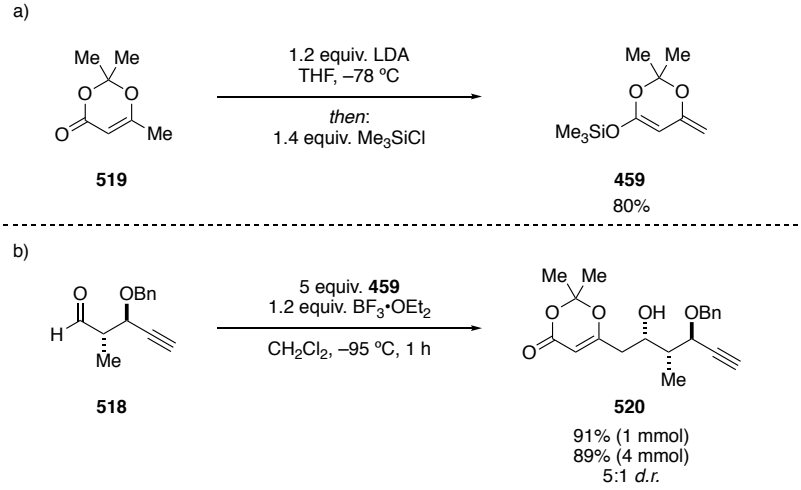
[a] yields and diastereomeric ratios determined on isolation; [b] work-up performed between steps 1 and 2.

Table 36 – Assay of dihydroxylation/periodate cleavage conditions

3.5.3. Efforts towards iodonium salt 471

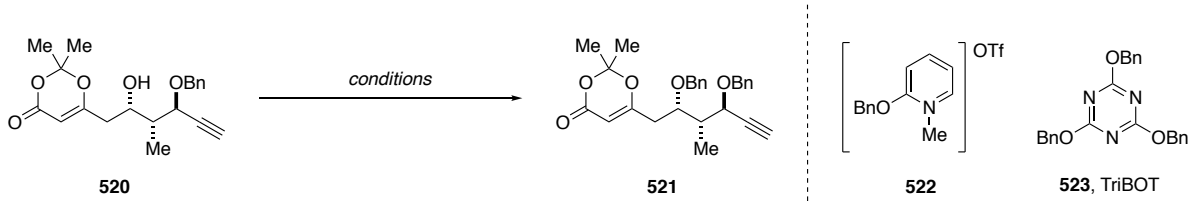
Dioxinone-derived vinylogous enol silane **459** was prepared (Scheme 104a),[199] and was then directly coupled to aldehyde **518** with treatment of the reaction mixture with boron trifluoride diethyl etherate at −95 °C (Scheme 104b).[178] When performed on an initial 1.0 mmol scale, this aldol reaction gave the

desired product in an excellent 91% yield and in a synthetically useful 5:1 *d.r.*. Reproducing the reaction on a 4.0 mmol scale gave 89% product formation with the same diastereoselectivity. A pleasing 76% isolated yield of diastereopure isomer **520** was achieved following chromatographic purification of the larger-scale reaction.



Scheme 104 – a) Synthesis of nucleophile **459**;[199] b) Synthesis of aldol adduct **520** by a vinylogous Mukaiyama aldol reaction with aldehyde **518** and nucleophile **459**.

Work next focused on the benzyl protection of aldol-derived secondary alcohol **520**. Four distinct benzylation conditions were tested to effect this transformation (Table 37). Disappointingly, decomposition was observed on exposure of **520** to classical benzylation conditions, Groth's benzyl trichloroacetamidate method and Dudley's pyridinium salt methodology (entries 1–3).[196,200,201] However, conversion to the desired product was observed with the use of Kunishima's acid catalysed benzylation using TriBOT (**523**) (entry 4, 18% yield by NMR after 5 h). Disappointingly, further extending the reaction time to 22 hours gave only a moderate improvement in yield (25%) with no starting material remaining (entry 5).



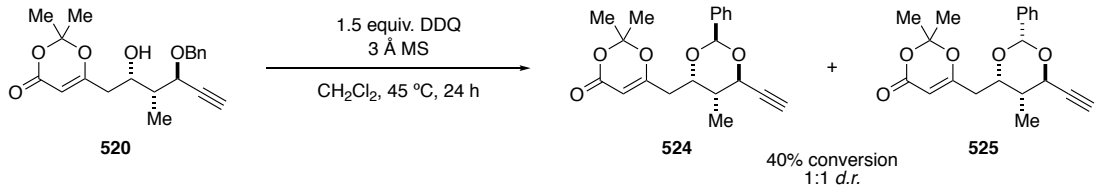
Entry	Conditions	Result
1[196]	1.2 equiv. NaH, 10 mol% TBAI, 1.4 equiv. BnBr DMF, 0 °C to rt, 18 h	**520** decomposition

2[200]	1.5 equiv. BnOTCA, 20 mol% TMSOTf CH_2Cl_2, 0 °C to rt, 24 h	**520** decomposition
3[201]	2 equiv. **522**, 2 equiv. MgO $PhCF_3$, 83 °C, 24 h	**520** decomposition
4[202]	0.4 equiv. TriBOT (**523**), 5 Å MS, 0.2 equiv. TfOH 1,4,-dioxane, rt, 5 h	18% yield[a]
5[202]	0.4 equiv. TriBOT (**523**), 5 Å MS, 0.2 equiv. TfOH 1,4,-dioxane, rt, 22 h	25% yield

[a] determined by ^{1}H NMR using 1,3,5-trimethoxybenzenetricarboxylate

Table 37 – Assay of benzylation conditions

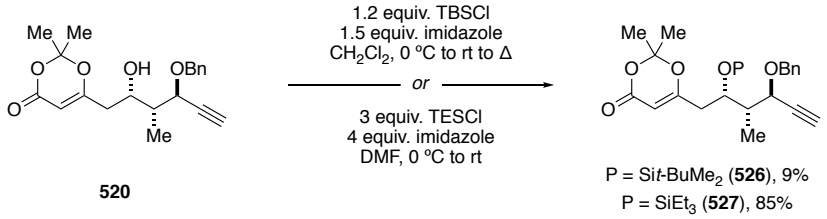
As no benzylation conditions could be identified that gave good yields of the desired product **521**, alternative alcohol protecting groups were evaluated. Use of a benzylidene acetal was considered advantageous as no modification to our original synthetic strategy would be required as such a group could be removed by hydrogenation.[203] In line with Oikawa's method for the generation of PMB acetals,[204] it was thought that the benzylidene acetal could be produced by intramolecular reaction of the secondary alcohol with the previously-installed benzyl group. Compound **521** was therefore oxidised with DDQ under anhydrous conditions to give 40% conversion to the acetal product after 24 hours (Scheme 105). Unfortunately, attempting to improve conversion by increasing the reaction temperature (70 °C, 1,2-dichlorethane) resulted in complete decomposition of the starting material and gave no further product formation. Moreover, it was disappointing to note that these reactions both gave a 1:1 ratio of diastereoisomers **524** and **525**, precluding the use of the benzylidene acetal protection strategy in our synthetic route.



Scheme 105 – Formation of benzylidene acetals **524** and **525**

The use of silyl protecting groups were next investigated (Scheme 106). Efforts to TBS protect the secondary alcohol furnished the corresponding silylated product in low yield (9%), likely due to the sterically demanding substrate/reagent combination. However, treatment of alcohol **520** with 3 equivalents of triethylsilyl chloride and 4 equivalents of imidazole gave the desired TES-protected

product in 85% yield, demonstrating that this sterically constrained substrate can be protected with some silyl groups.



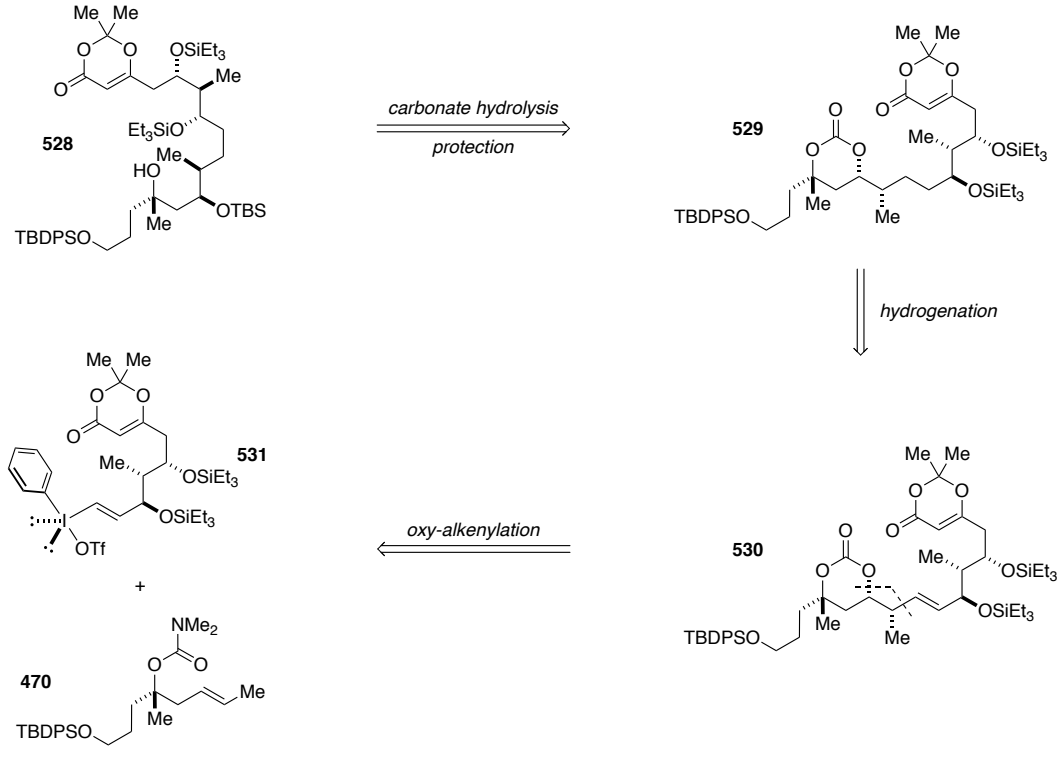
520

Scheme 106 – Silyl protection of **520**

It was recognised that the use of a mixed silyl-/benzyl-protected system would require inelegant functional group manipulations later in the synthesis. The synthetic strategy was therefore re-evaluated.

3.6 Second Generation Synthetic Strategy

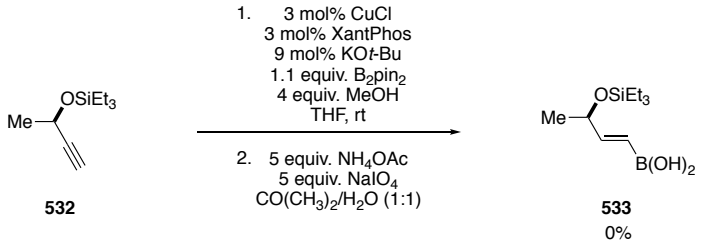
As it was shown that triethylsilyl groups, unlike benzyl groups, may be installed to protect sterically-demanding secondary alcohols, efforts next focused on the synthesis of bis-silylated iodonium salt **531** (Scheme 107). Advantageously, this modification would avoid the need to re-protect the secondary alcohols of **530** following hydrogenation of fragment-coupled linear precursor **529**.



Scheme 107 – Proposed retrosynthesis from intermediate **528** to the key fragment union step

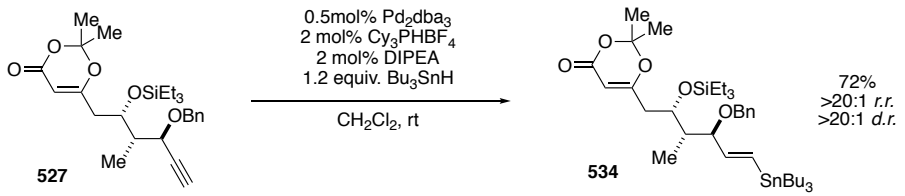
3.6.1. Initial studies

To minimise the consumption of valuable advanced intermediates, initial studies focused on the generation of model alkenyl(aryl)iodonium salts for the desired fragment **531**. The tolerance of triethylsilyl-protected model substrate **532** to the alkyne borylation/oxidation procedure was first tested (Scheme 108). Disappointingly, complete starting material decomposition was observed following oxidative hydrolysis, indicating such a route to be unsuitable for our synthetic strategy.



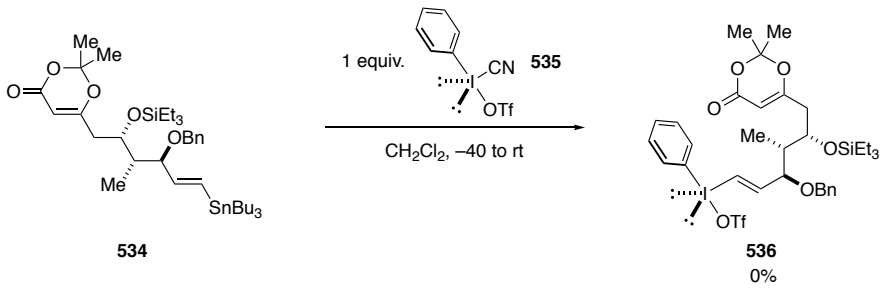
Scheme 108 – Test borylation on model silane **532**

It was considered that Stang's procedure for the synthesis of iodonium salts from vinyl stannanes may provide an effective alternative route to fragment iodonium salt **531**.[205] Model benzyl/triethylsilyl alkyne **527** was accordingly hydrostannylated using a sterically-demanding palladium catalyst to give the desired *E*-vinyl stannane in 72% yield and complete regio- and diastereoselectivity (Scheme 109).[206]



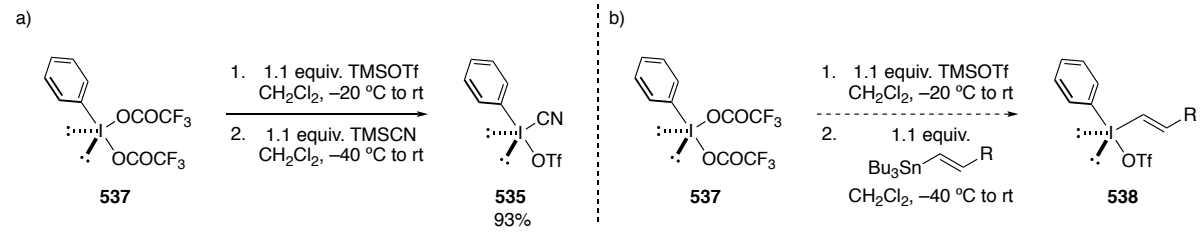
Scheme 109 – Hydrostannylation of alkyne **527**

Stang's cyanated iodane precursor **535** was then prepared and mixed with stannane **534**. Disappointingly no formation of the corresponding iodonium salt was observed (Scheme 110).[205] LCMS analysis indicated that both benzyl and silyl protecting groups were lost under the reaction conditions, possibly due to attack by the cyanide group of precursor **535**.

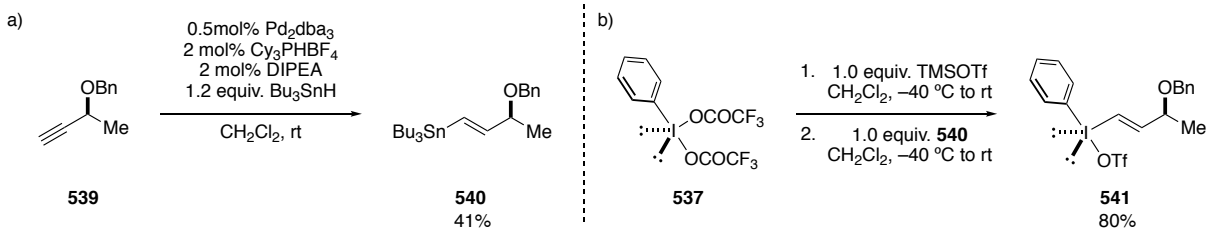


Scheme 110 – Attempted conversion of **534** to iodonium salt **536**

It was questioned whether Stang's procedure for the generation of iodane **535** (Scheme 111a) could be modified to furnish alkenyl(aryl)iodonium salts directly from PIFA and a vinyl stannane (Scheme 111b). Benzyl-substituted vinyl-stannane **540** was synthesised to test the viability of this one-pot iodonium salt-formation strategy (Scheme 112a), chosen as it was anticipated that a benzyl group would be more stable than a triethylsilyl group under Lewis acidic conditions. Gratifyingly, it was observed that adding stannane **540** at –40 °C to a pre-mixed solution of PIFA and TMSOTf led to the production of the desired alkenyl(phenyl)iodonium salt **541** in 80% isolated yield (Scheme 112b).

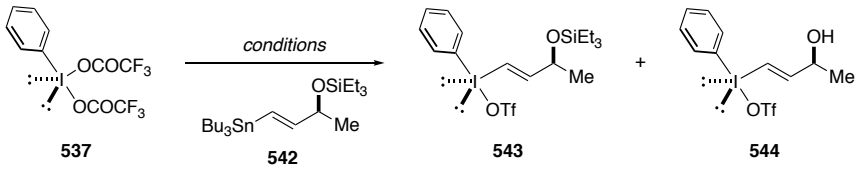


Scheme 111 – a) Synthesis of Stang's iodonium precursor; b) application to a one-pot iodonium salt formation reaction from PIFA (**537**)



Scheme 112 – a) Synthesis of vinyl-stannane **540**; b) conversion to iodonium salt **541**

The same method for alkenyl(aryl)iodonium salt generation was next applied to the synthesis of TES-protected iodane **543** (Table 38). Disappointingly, initial exposure of stannane **542** to the mixture of PIFA and trimethylsilyl triflate gave a 5:1 crude ratio of the desilylated iodonium salt **544** to the desired product (entry 1). Pleasingly, production of **543** could be biased with the use of triethylsilyl triflate as the Lewis acidic promoter (entry 2, 82:18 ratio of **543** to **544**).



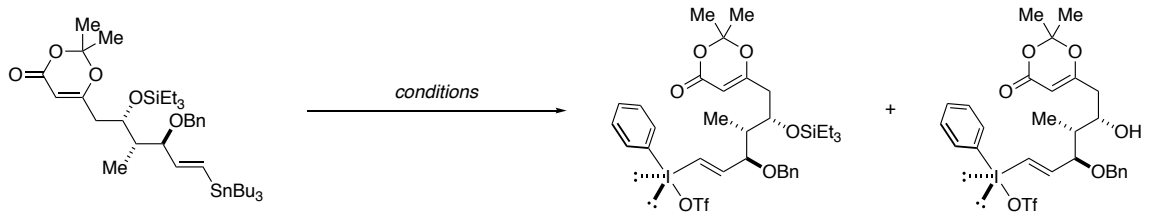
537 542 543 544

Entry	Conditions	Ratio / %[a]		
		543	**544**	**542**
1[b]	1. 1.0 equiv. **TMS**OTf, CH_2Cl_2, –40 °C to rt 2. 1.0 equiv. **542**, CH_2Cl_2, –40 °C to rt	17	83	0
2[c]	1. 1.0 equiv. **TES**OTf, CH_2Cl_2, –40 °C to rt 2. 1.0 equiv. **542**, CH_2Cl_2, –40 °C to rt	82	18	0

[a] calculated from crude ^{1}H NMR; [b] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzenetricarboxylate as 74% **544** and 15% desired **543**; [c] 12% **543** was isolated by silica column chromatography.

Table 38 – Formation of iodonium salt **543**

Formation of the fragment-like mixed benzyl/triethylsilyl protected iodonium salt **536** was next surveyed (Table 39). Whilst the combination of PIFA and TESOTf with stannane **534** (entry 1) gave full conversion of the starting material, the presence of desilylated iodonium salt **545** as the major product was observed, attributed to the presence of acid in the reaction mixture. The reaction was therefore next performed in the presence of anhydrous sodium carbonate to neutralise any effects of acid formation. Use of this base gave 35% conversion to **536** with no apparent decomposition to the desilylated analogue (entry 2). Increasing the equivalents of the reagents (1.2 equiv., entry 3) gave increased production of **536** (45%) with only traces of desilylation. Finally, increasing the reagent equivalents further (3 equiv. TESOTf and PIFA) whilst maintaining excess base (15 equiv.) led to 70% conversion to the desired product with 30% **545** (entry 4). Chromatographic purification of this latter product mixture led to the isolation of only 8% **536**, indicating purification to be problematic despite the neutralisation of the reaction mixture with sodium carbonate. With the insight gathered so far, it was decided that the problem of iodonium salt instability should be addressed during investigations into the formation of the desired *bis*-silylated iodonium fragment **531**.



534 **536** **545**

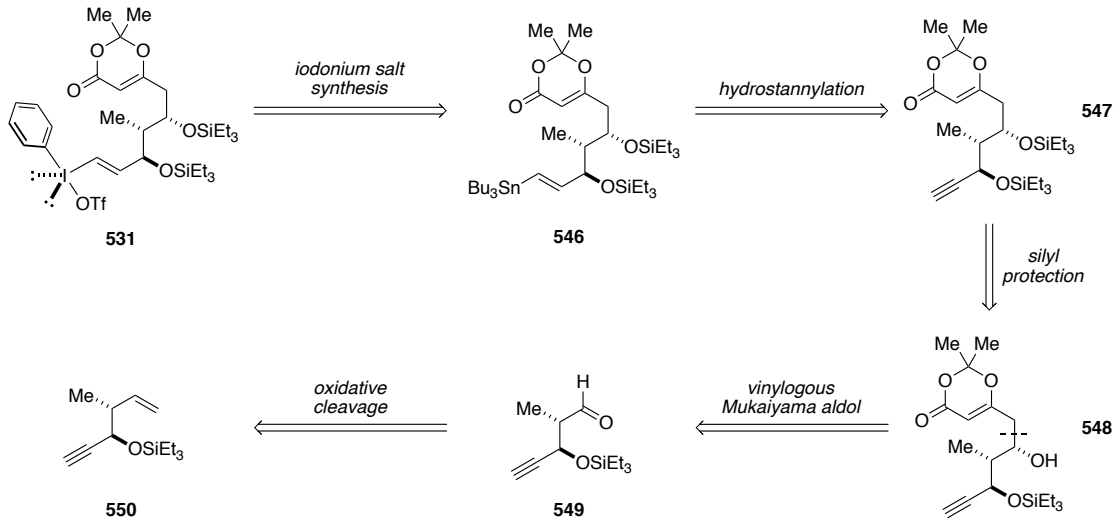
Entry	Conditions	Ratio / %[a]		
		536	**545**	**534**
1	1. 1.0 equiv. PIFA and TESOTf, CH_2Cl_2, −40 °C to rt 2. 1.0 equiv. **534**, CH_2Cl_2, −40 °C to rt	25	75	0
2	1. 1.0 equiv. PIFA and TESOTf, 5.0 equiv. Na_2CO_3, CH_2Cl_2, 0 °C to rt 2. 1.0 equiv. **534**, CH_2Cl_2, −78 °C to rt	35	0	65
3	1. 1.2 equiv. PIFA and TESOTf, 6.0 equiv. Na_2CO_3, CH_2Cl_2, 0 °C to rt 2. 1.0 equiv. **534**, CH_2Cl_2, −78 °C to rt	45	3	52
4[b]	1. 3.0 equiv. PIFA and TESOTf, 15 equiv. Na_2CO_3, CH_2Cl_2, 0 °C to rt 2. 1.0 equiv. **534**, CH_2Cl_2, −78 °C to rt	70	30	0

[a] calculated from crude ^{1}H NMR; [b] 8% **536** was isolated following silica column chromatography.

Table 39 – Formation conditions for iodonium salt **536**

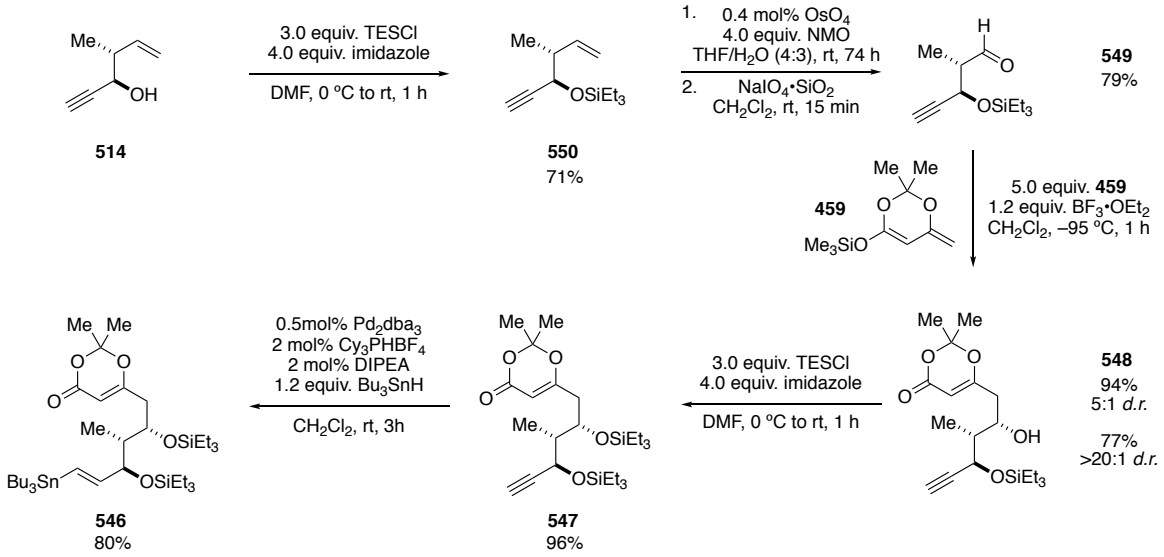
3.6.2. Forwards synthesis

As a result of the studies outlined in sections 3.5.3 and 3.6.1, the synthetic strategy was amended both to utilise triethylsilyl protecting groups and to employ a vinyl stannane as the nucleophilic precursor to the iodonium salt (Scheme 113).



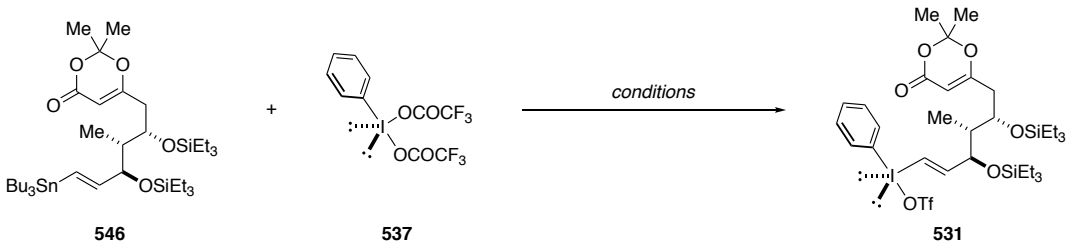
Scheme 113 – Second-generation retrosynthetic analysis to **531**

Vinyl stannane **546** was generated in five synthetic steps from crotylated alcohol **514** (Scheme 114). Protection of **514** using TESCl and imidazole furnished the desired triethylsilyl ether **550** in 71% yield. The alkene group then underwent an osmium-catalysed dihydroxylation over three days before exposure to solid-supported sodium periodate, giving aldehyde **549** in 79% yield and with excellent retention of the α-stereochemistry. The aldehyde was directly exposed to a vinylogous Mukaiyama aldol reaction with dioxinone nucleophile **459** to give the desired aldol adduct in 94% yield and in 5:1 *d.r.*. Purification yielded the desired diastereomerically pure product **548** in 77% yield. A subsequent TES protection of the secondary alcohol was carried out to give **547** in an excellent 96% yield. Finally, the alkyne of **547** underwent a diastereo- and regioselective hydrostannylation using a palladium catalyst to furnish the target alkenyl-tin compound **546** in 80% yield.



Scheme 114 – Forward synthesis of vinyl stannane **546** from alcohol **514**

With stannane **546** in hand, investigations proceeded to the generation of the desired *bis*-triethylsilyl substituted iodonium salt **531** (Table 40). Although high levels of starting material conversion to the desired product (84%) were observed on exposure of the stannane to a solution of excess PIFA, TESOTf and sodium carbonate (entry 1), all efforts to isolate the resulting iodonium salt were unsuccessful. It was considered that the iodonium salt may desilylate when separated from the insoluble base as any acid formed would no longer be neutralised. The reaction was therefore performed with the use of the non-nucleophilic and soluble base di-*tert*-butyl pyridine (DTBP) (entry 2), ultimately allowing 38% product to be isolated for the first time as a mixture with the pyridine base.



546 **537** **531**

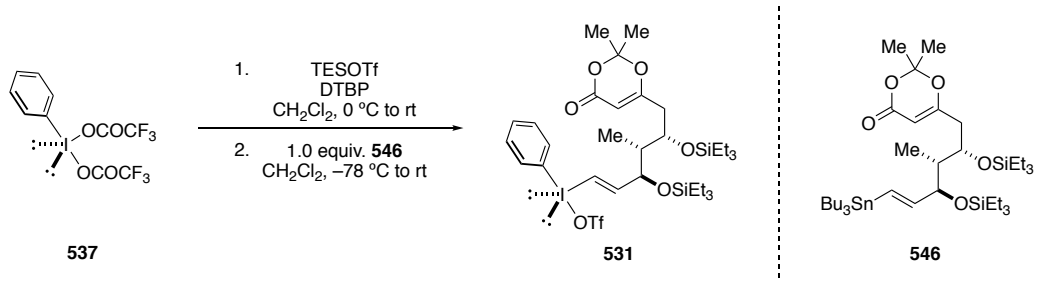
Entry	Conditions	Ratio / %[a,b]	
		531	**546**
1	1. 3.0 equiv. PIFA and TESOTf, 15 equiv. Na_2CO_3 CH_2Cl_2, 0 °C to rt 2. 1.0 equiv. **546**, CH_2Cl_2, −78 °C to rt	84 (0)	-
2	1. 4.0 equiv. PIFA, TESOTf and DTBP CH_2Cl_2, 0 °C to rt 2. 1.0 equiv. **546**, CH_2Cl_2, −78 °C to rt	86 (38)	-

[a] calculated from crude ^{1}H NMR; [b] bracketed quantity denotes isolated yield following chromatography

Table 40 – Formation conditions for iodonium salt **531**

It was hoped that the use of an intermediate aqueous work-up prior to chromatographic purification of the iodonium salt would slow any acid-catalysed decomposition processes by removal of acid into the aqueous phase (Table 41, entries 1–3). Disappointingly, quenching the reaction with saturated sodium bicarbonate solution (entry 2) gave 20% eliminated alkyne **547** and a 60% NMR yield of the desired product, lower than the 80% yield recorded for the control reaction (no work-up, entry 1). However, it was gratifying to observe that quenching with water (entry 3) furnished improved iodonium salt stability in NMR solvent and gave only a marginally reduced 78% NMR yield.

Next investigating reagent equivalents, it was observed that superior product yields could be achieved with three equivalents each of PIFA, DTBP and TESOTf (85% yield following extraction, entry 4). Reduced yields and incomplete starting material conversions were observed with lower reagent equivalencies (entries 5 and 6). Finally, attempts were made to isolate the desired complex iodonium fragment by chromatographic purification. Although alumina chromatography (entry 7) was observed to give poor iodonium salt recovery, we were delighted to note that isolation of the iodonium salt could be achieved from silica, giving the desired salt in a very good 76% yield (entry 8). However, it was disappointing to observe that even purified iodonium salt **531** rapidly decomposes on standing.



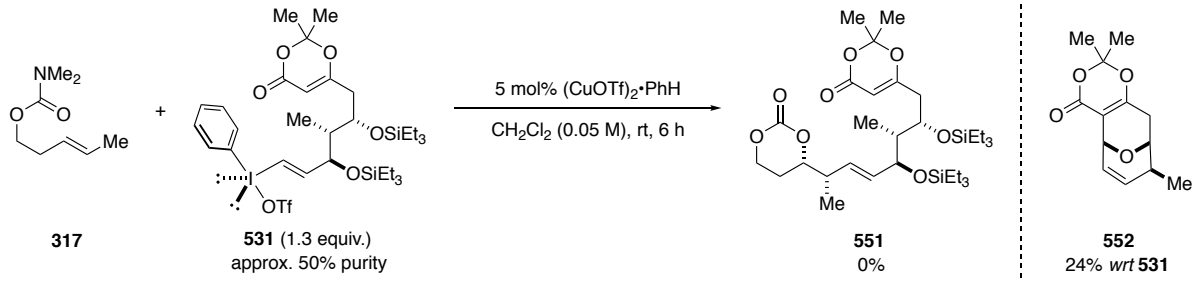
537 **531** **546**

Entry	Equivs. PIFA, DTBP and TESOTf	Scale / µmol	Purification[a]	Yield 531 / %[b]
1	4.0	10	-	80
2	4.0	10	$NaHCO_3/CH_2Cl_2$	60 (20% **547**)
3	4.0	20	H_2O/CH_2Cl_2	78
4	3.0	10	H_2O/CH_2Cl_2	85
5	2.0	10	H_2O/CH_2Cl_2	75
6[c]	1.0	10	H_2O/CH_2Cl_2	17
7[d]	3.0	50	H_2O/CH_2Cl_2 Al_2O_3 column	85 (14)
8	3.0	50	H_2O/CH_2Cl_2 SiO_2 column	89 (76)

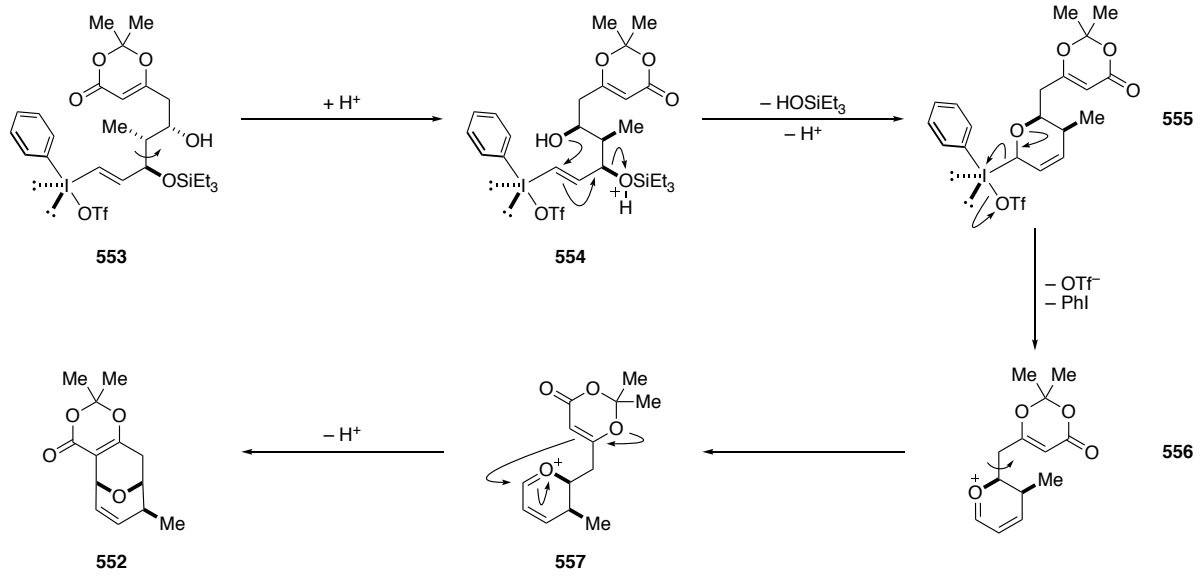
[a] Work up conditions with chromatographic solid phase given if applicable; [b] yield determined by ^1H NMR using 1,3,5-trimethoxybenzenetricarboxylate, bracketed quantity indicates isolated yield; [c] 55% starting material **546** observed by ^1H NMR; [d] 7% alkyne **547** co-eluted with product

Table 41 – Further optimisation of formation conditions for iodonium salt **531**

Despite the instability, iodonium salt **531** was tested in a model copper-catalysed *oxy*-alkenylation process with substrate **317** (Scheme 115). Although there was no apparent evidence for the conversion of the starting materials to the desired coupled product **551**, tricylic product **552** was observed and was obtained in 24% isolated yield with respect to the introduced iodonium salt. A proposed acid-catalysed mechanism for the formation of this tricycle from monodesilylated adduct **553** is outlined below (Scheme 116).

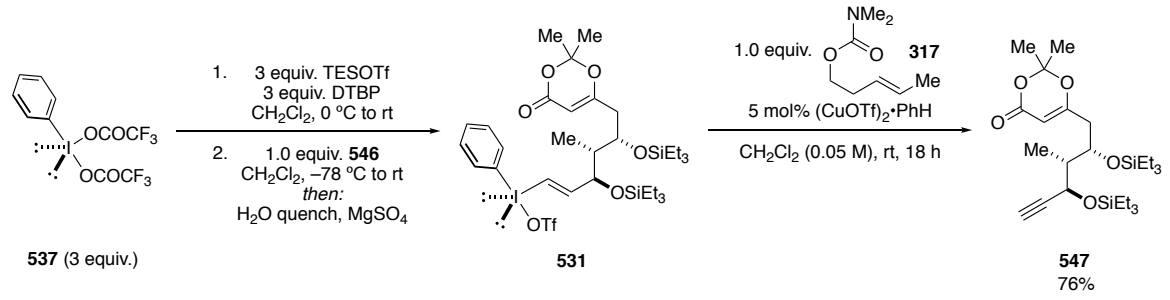


Scheme 115 – Attempted coupling of model substrate **317** and iodonium salt **531**

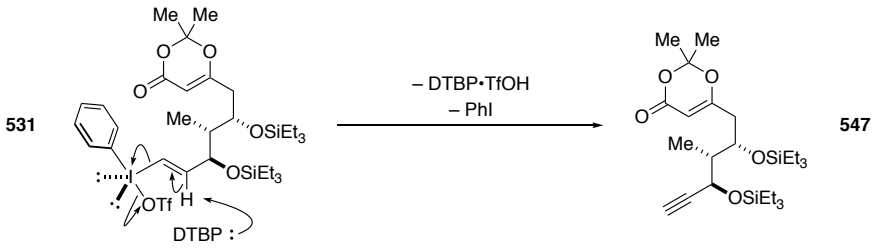


Scheme 116 – Proposed mechanism for the generation of cyclised product **552**

The coupling of model substrate **317** to iodonium salt **531**, used directly following work-up of the iodonium salt, was next tested. It was anticipated that the presence of residual DTBP would preclude the formation of tricycle **552** by removing acid from the system (Scheme 117). Disappointingly, only the production of alkyne **547** was observed from the crude product mixture, presumed to be generated through the *syn*-elimination of the iodonium salt (Scheme 118).

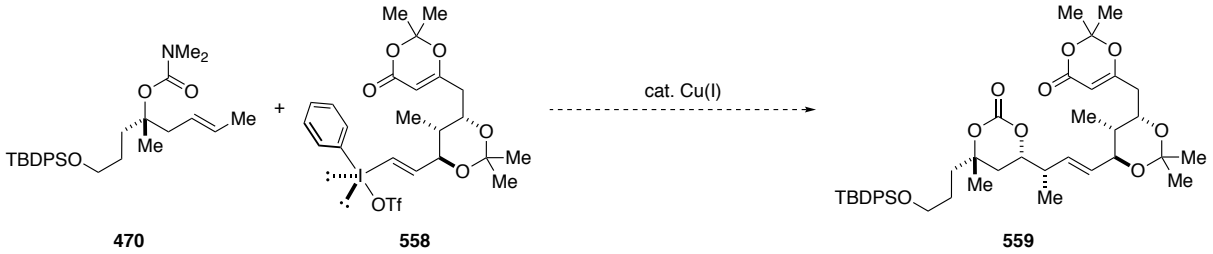


Scheme 117 – Proposed two-step iodonium salt formation copper-catalysed alkene *oxy*-alkenylation



Scheme 118 – Proposed *syn*-elimination of **531**

The studies discussed in this section indicate iodonium salt **531** to undergo decomposition processes faster than fragment coupling. Furthermore, the triethylsilyl groups of this iodonium salt appear to be particularly vulnerable to deprotection. As Dean Holt previously has showed that acetonides can be tolerated under *oxy*-alkenylation conditions (Scheme 96, page 89),[186] attention was next turned to the use of this protecting group in our synthetic route. The strategy was accordingly modified towards the coupling of homoallylic carbonate southern fragment **470** to an acetonide-protected iodonium salt such as **558** (Scheme 119).

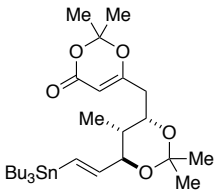


Scheme 119 – Third generation iodonium salt **558** for coupling to southern fragment **470**

3.7 Third Generation Synthetic Strategy

3.7.1. Synthesis of vinyl stannane 560

It was planned to access acetonide-protected iodonium salt **558** from vinyl stannane **560** (Figure 11). Although it was thought that this key stannane could be accessed by modifying the route detailed in section 3.5.3, efforts were first directed towards the attempted development of synthetic routes that were thought to provide higher-yielding and more rapid access to the advanced alkenyl-tin intermediate.

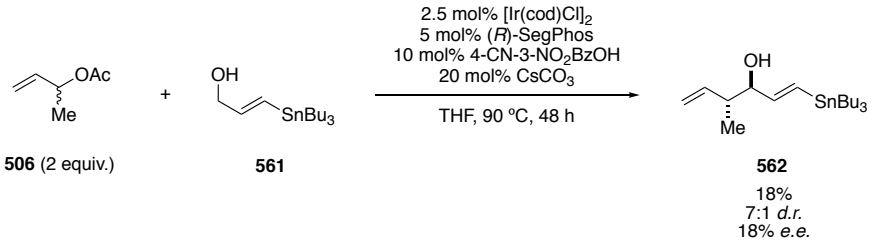


560

Figure 11 – Target vinyl stannane **560**

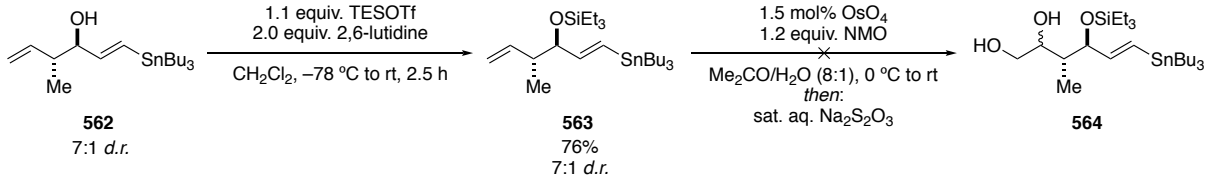
3.7.1.1 Crotylation of stannylated substrates

Seeking to avoid the need for alkyne desilylation and a late-stage hydrostannylation, it was questioned whether a vinyl-stannane functionality may be carried through our synthesis. As allylic alcohols are tolerated under Krische's crotylation process,[190] stannylated alcohol **561** underwent iridium-catalysed transfer hydrogenation to furnish the crotylated product **562** in 18% yield, 7:1 *d.r.* and 18% *e.e.* (Scheme 120).



Scheme 120 – Krische crotylation of stannylated allylic alcohol **561**

Despite the low yield and enantioenrichment obtained using Krische's methodology, efforts were made to silyl protect and dihydroxylate the crotylated product. Disappointingly, although treatment of alcohol **561** with triethylsilyl triflate gave the TES-protected product **563** in good yield, dihydroxylation with osmium tetroxide led to complete starting material decomposition (Scheme 121). Introduction of the vinyl stannane functionality at an early stage in the synthesis was therefore not pursued further.

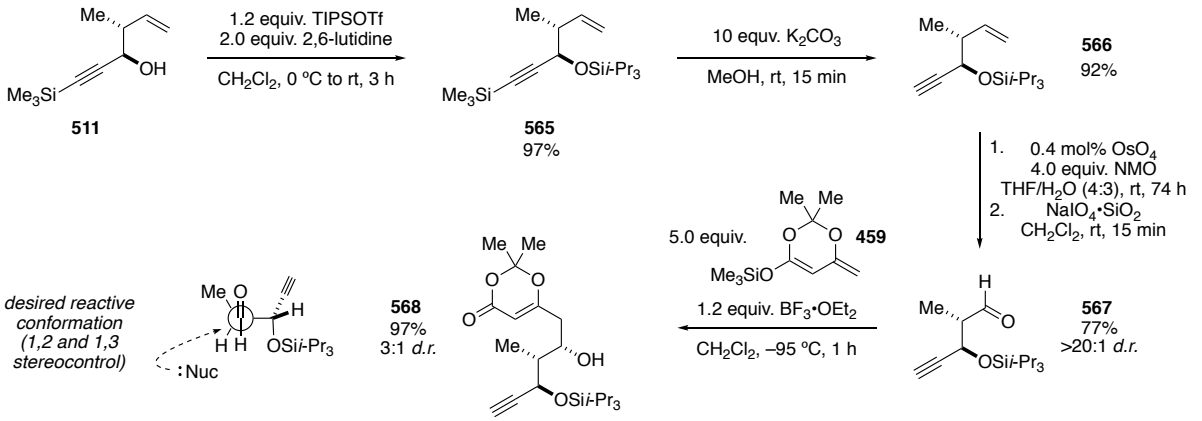


Scheme 121 – TES protection and attempted dihydroxylation of crotylated product **562**

3.7.1.2 Alternative silyl protection

Returning to the original crotylation strategy, it was thought that tri-*iso*-propylsilyl protection of the secondary alcohol **511** would allow for the removal of the acetylenic trimethylsilyl group without the danger of product volatility. Further, it was considered that the increased steric bulk of the protecting

group may provide improved diastereoselectivity for the later vinylogous Mukaiyama aldol reaction. This was thought as, by evaluating aldehyde **567**, it can be seen that both 1,2- (Felkin-Anh) and 1,3- (Evans) models reinforce the desired stereochemical outcome of the vinylogous Mukaiyama aldol reaction.[207] Crotyl alcohol **511** was therefore reacted with TIPSOTf to furnish the corresponding tri-*iso*-propylsilylether **565** in 97% yield (Scheme 122). As predicted, treatment of **565** with potassium carbonate in methanol gave the corresponding monosilylated enyne product in an excellent 92% yield with easy product recovery. Alkene **566** then underwent the previously-developed osmium-catalysed dihydroxylation/periodate cleavage sequence to generate aldehyde **567** in 77% yield and with minimal α-epimerisation. However, despite the observation of a high yield, the addition of dioxinone nucleophile **459** to the aldehyde furnished the desired aldol adduct in only 3:1 *d.r.*, too low to be synthetically useful.



Scheme 122 – Investigation into the use of TIPS alcohol protection in the early steps of the synthesis

It was next thought that by installing a bulky acetylenic group on aldehyde **567**, the reactive conformation leading to the minor Mukiyama aldol product would be further disfavoured, thereby giving improved diastereoselectivity (Figure 12). A TIPS group was chosen as the bulky group as, should the strategy be successful, the total synthesis could instead begin with the tri-*iso*-propylsilyl substituted propargyl aldehyde.

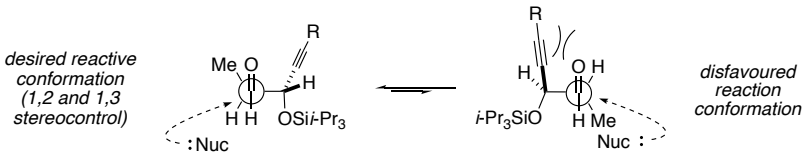
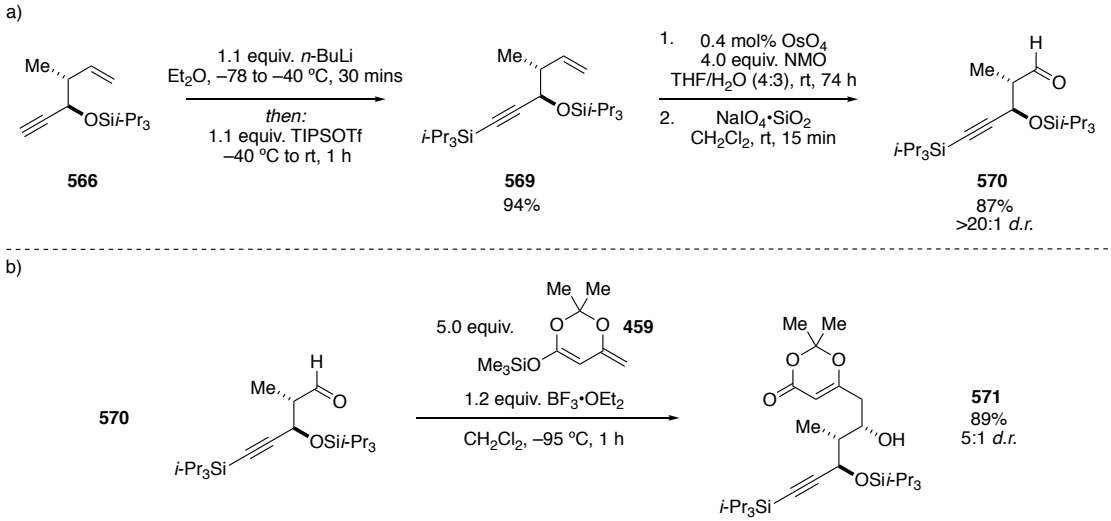


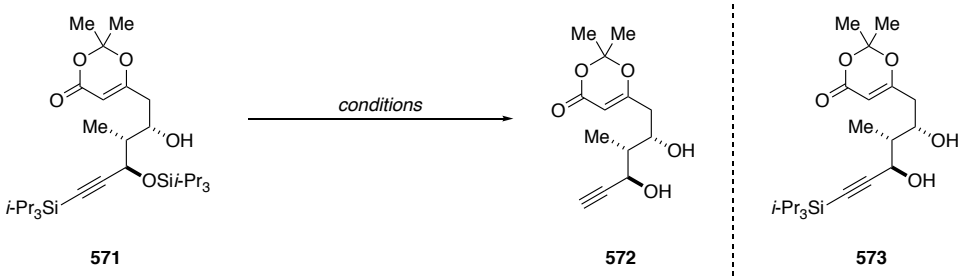
Figure 12 – Stereochemical prediction of Mukaiyama aldol selectivity

TIPS bearing aldehyde **570** was prepared from **566** by an acetylenic tri-*iso*-propylsilylation, an alkene dihydroxylation and an oxidative cleavage in 82% overall yield (Scheme 123a). Aldehyde **570** then underwent reaction with nucleophile **459** to furnish Mukaiyama aldol adduct **571** in 89% yield and in an improved but inseparable 5:1 *d.r.* (Scheme 123b).



Scheme 123 – a) Generation of aldehyde **530** and b) Mukaiyama aldol reaction toward aldol adduct **571**

Attempts were next made to remove the two tri-*iso*-propylsilyl groups from **571**. It was considered that diol **572** could then be converted to the acetonide-protected alkyne required for synthesis of vinyl stannane **560**. Disappointingly, all efforts to deprotect **571** with TBAF led to either starting material decomposition or the formation of only mono-deprotected derivative **573** (Table 42).[208] Owing to this challenging desilylation, no further investigations were carried out towards the generation of vinyl stannane **560** using TIPS groups as either acetylenic or alcoholic protecting groups.



Entry	Conditions	Yield / %[a]		
		572	**573**	**571**
1[b]	2.4 equiv TBAF•3H_2O, THF, 0 °C, 1 h	0	80	0
2[c]	2.4 equiv TBAF•3H_2O, THF, 0 °C, 2 h	0	45	0
3	2.2 equiv TBAF (1M in THF), THF, 0 °C to rt, 18 h	0	0	0
4	2.2 equiv TBAF (1M in THF), THF/H_2O, 0 °C to rt, 72 h	0	70	0

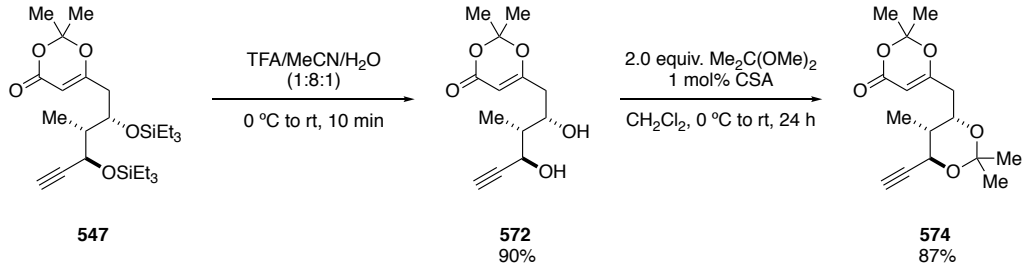
5	4.0 equiv TBAF (1M in THF), THF/H_2O, 0 °C to rt, 192 h	0	44	0

[a] yield determined by ^1H NMR using mesitylene as an internal standard; [b] using 1,3,5-trimethoxybenzenetricarboxylate; [c] isolated yield

Table 42 – Unsuccessful attempts to deprotect aldol adduct **571**

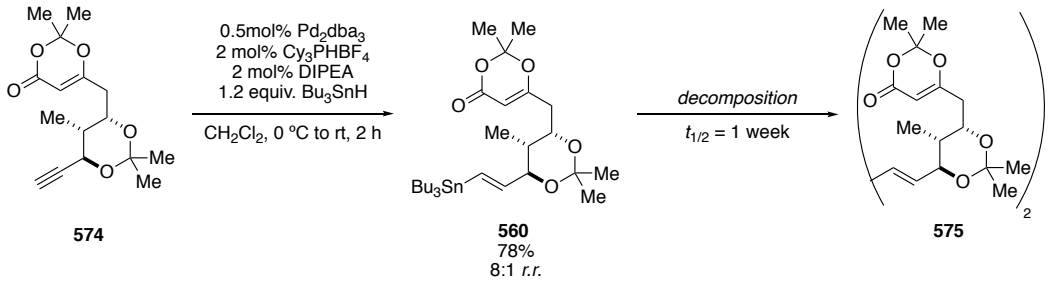
3.7.1.3 Desilylation of intermediate **547**

Following the unsuccessful explorations of alternative synthetic routes to vinyl stannane **560**, efforts were directed towards the production the key stannane from TES-protected advanced intermediate **547**. To this end, alkyne **547** was treated with TFA to give intermediate diol **572** in an excellent 90% yield.[209] The diol product was then reacted with 2,2-dimethoxypropane in the presence of an acid catalyst to give acetonide-protected alkyne **574** in 87% yield (Scheme 124).[210]



Scheme 124 – Generation of acetal-protected alkyne **574**

Alkyne **574** was then hydrostannylated using a sterically-demanding palladium catalyst to afford the vinyl stannane **560** in 78% yield and complete diastereoselectivity (Scheme 125). However, it was disappointing to note that the alkenyl-tin compound was produced in an inseparable 8:1 mixture of regioisomers, attributable to the relatively low steric demands of the acetonide group. Further, product **560** was observed to undergo homodimerisation with a half-life of approximately one week. The vinyl stannane was therefore used in the subsequent iodonium salt formation shortly following its production.

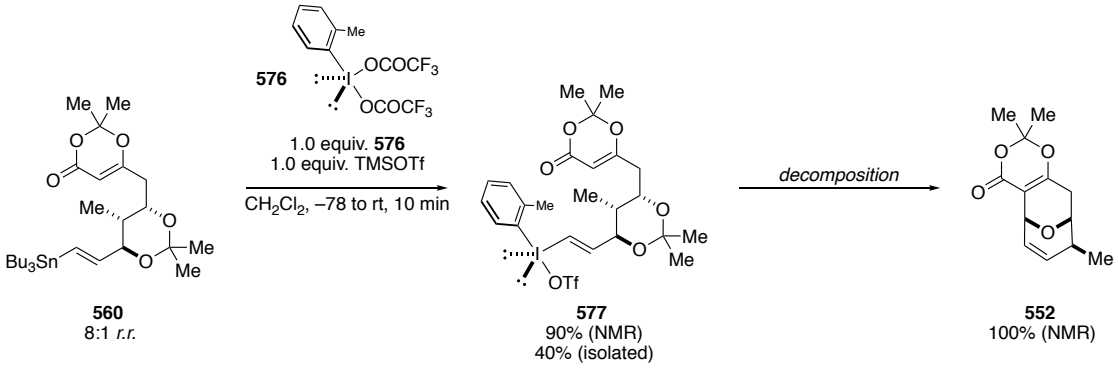


Scheme 125 – Hydrostannylation of terminal alkyne **574** to furnish vinyl stannane **560**

3.7.2. Formation of iodonium salt 558

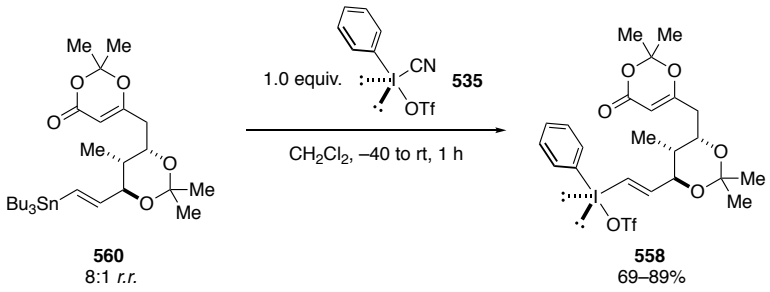
Previous work within the Gaunt group has demonstrated that only terminal vinyl stannanes can be converted to iodonium salts.[186] As such, the regioisomeric mixture of **560** was directly exposed to a

mixture of *ortho*-tolyliodoniumditrifluoroacetate **576** and TMSOTf to give a 90% crude yield of iodonium salt **577** (Scheme 126). Disappointingly, despite using an *ortho*-tolyl group to increase the iodane stability, only 40% product could be isolated following purification. Moreover, the iodonium salt was found to rearrange to tricylic adduct **552** on standing in NMR solvent. Residual acid formed during the reaction was suspected to catalyse this cyclisation process.



Scheme 126 – Formation and decomposition of iodonium salt **577**

It was anticipated that Stang's method for the generation of iodonium salts would preclude the formation of cyclised product **552** as no Lewis acid is present in the reaction.[205] Gratifyingly, reaction of vinyl stannane **560** with cyanated iodane **535** led to the formation of the desired iodonium salt **558** in a good yields following chromatographic purification (Scheme 127). Furthermore, **558** could be precipitated on treatment with hexanes to enable storage of the iodonium salt at −18 °C. To the best of our knowledge, **558** represents the most complex alkenyl iodonium salt synthesised to date.

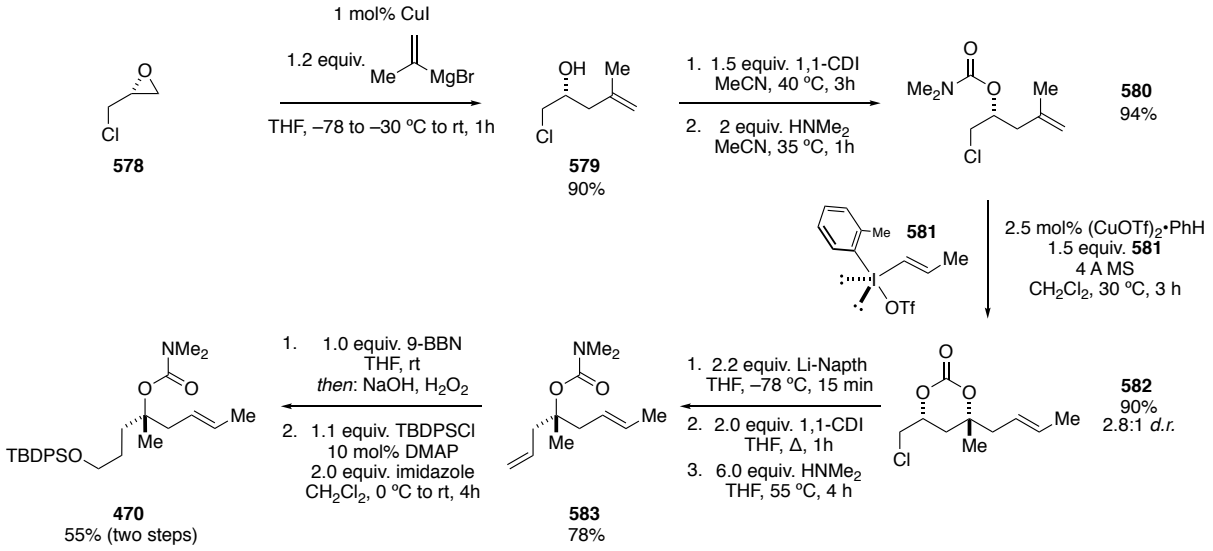


Scheme 127 – Formation of iodonium salt **558** by Stang's method[205]

3.7.3. Southern fragment synthesis (Dean Holt and Dominik Reich)

Dean Holt and Dominik Reich worked together to develop the following synthesis of southern fragment **470** (Scheme 128).[186,211] Starting from (*R*)-epichlorohydrin **578**, a copper(I) catalysed epoxide ring-opening with isopropenylmagnesium bromide furnished secondary alcohol **579** in an excellent 90% yield.[212] Subsequent treatment with 1,1-carbonyldiimidazole (CDI) and dimethylamine gave homoallylic carbamate **580** in 94% yield.[158] **580** then underwent a copper-catalysed *oxy*-alkenylation reaction with propenyl iodonium salt **581** to furnish homoallylic carbonate **582** in an excellent 90%

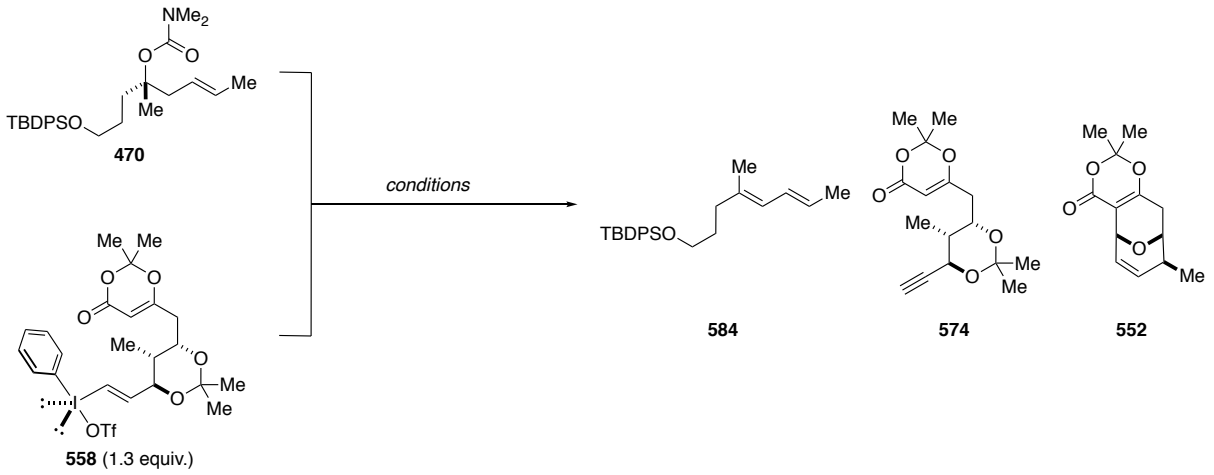
yield but in a low 2.8:1 *d.r.*. Although extensive investigations towards improving this reaction were carried out by Dominik Reich, no significant improvement in diastereoselectivity was observed.[211] Pleasingly, the product diastereoisomers formed in the *oxy*-alkenylation of **580** were found to be separable, allowing isolation of the desired *syn*-configured product. Carbonate **582** then underwent decarboxylation, induced by C–Cl bond reduction, to give an intermediate volatile alcohol that was directly carbamylated to furnish homoallylic carbamate **583** in 78% yield over three steps. Finally, a hydroboration/oxidation sequence was carried out on the terminal alkene portion of **583** with the resulting primary alcohol then TBDPS protected to give the southern fragment in 55% yield over two steps.



Scheme 128 – Synthesis of southern fragment **470** – Dominik Reich[211]

3.7.4. Coupling studies

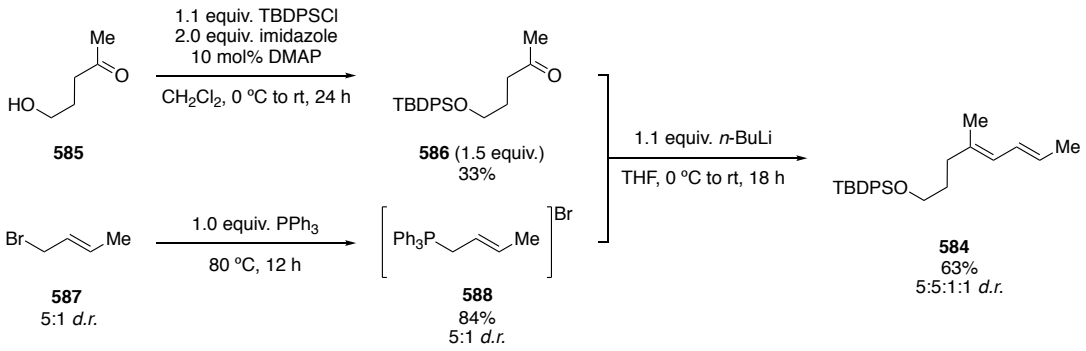
Finally, attention was turned towards the copper-catalysed coupling of our complex fragments to form the desired precursor to (–)-lyngbyaloside B. The conditions developed by Dean Holt (Scheme 65, page 41) were first applied towards this key fragment union, but were observed to give decomposition of the iodonium salt with no apparent coupling to the desired product (Table 43, entry 1). Interestingly, diene **584** was recovered in 32% yield from the reaction mixture, presumably formed *via* the elimination of the carbamoyl group from substrate **470**. The identity of this product was confirmed by a *de novo* synthesis (Scheme 129). Secondly, due to uncertainty over the reliability of the $(CuOTf)_2$•PhH, the catalytic combination of copper(I) iodide and silver triflate was tested for the desired *oxy*-alkenylation (entry 2). In addition to the production of diene **584**, this reaction gave a 47% crude yield of tricycle **552** but still produced no desired product. Sodium carbonate was then added to the reaction mixture in order to prevent the acid-mediated cyclisation. This reaction unfortunately led to the elimination of the iodonium salt and no starting material conversion (entry 3).



Entry	Conditions	Yield / %			
		470	**584**	**574**	**552**
1	5 mol% $(CuOTf)_2$•PhH CH_2Cl_2 (0.05 M), rt, 3 h	0	32	0	tr
2[a]	10 mol% CuI, 10 mol% AgOTf CH_2Cl_2 (0.05 M), rt, 24 h	0	40	0	47
3[a]	10 mol% CuI, 10 mol% AgOTf, 1.5 equiv. K_2CO_3 CH_2Cl_2 (0.05 M), rt, 5 h	100	0	94	0

[a] yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzenetricarboxylate as internal standard

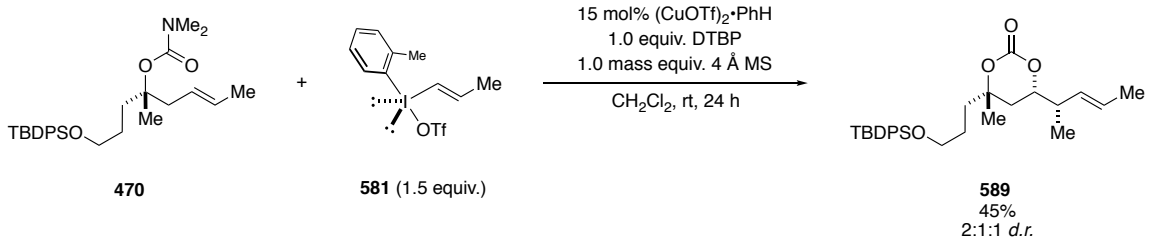
Table 43 – Initial attempts to couple fragments **470** and **558**



Scheme 129 – Formation of diene **584** *via* Wittig coupling of ketone **586** and phosphonium salt **584**

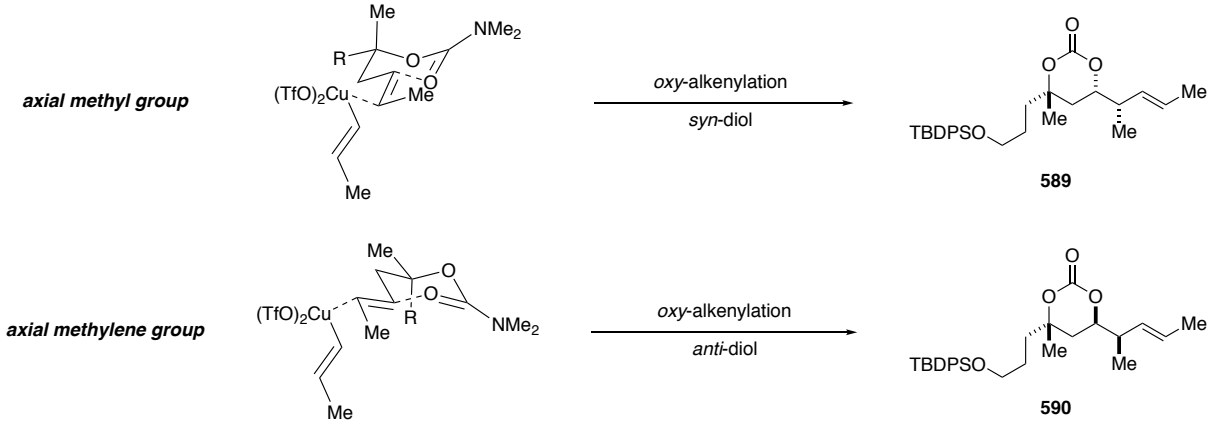
As both coupling partners were unstable in the tested copper-catalysed *oxy*-alkenylation reactions, little insight could be gained into how the coupling process should be optimised. As the carbamate substrate

was thought to be the more stable of the two fragments, it was questioned whether this carbamate would undergo the desired reaction with a simple iodonium salt, thereby allowing coupling conditions to be developed that would maximise the stability of the substrate. These conditions could then be applied to the key fragment union. Accordingly, Dominik Reich investigated the coupling of the southern fragment with propenyl iodonium salt **581**. Following extensive studies, it was discovered that the *oxy*-alkenylation could be effected with 30 mol% copper(I) triflate, one equivalent di-*tert*-butylpyridine and one mass equivalent of 4 Å molecular sieves. These conditions gave the desired carbonate in 45% yield and in an intractable mixture of diastereoisomers (Scheme 130).[213]



Scheme 130 – Coupling of southern fragment **470** with iodonium salt **581** (NMR) – Dominik Reich[213]

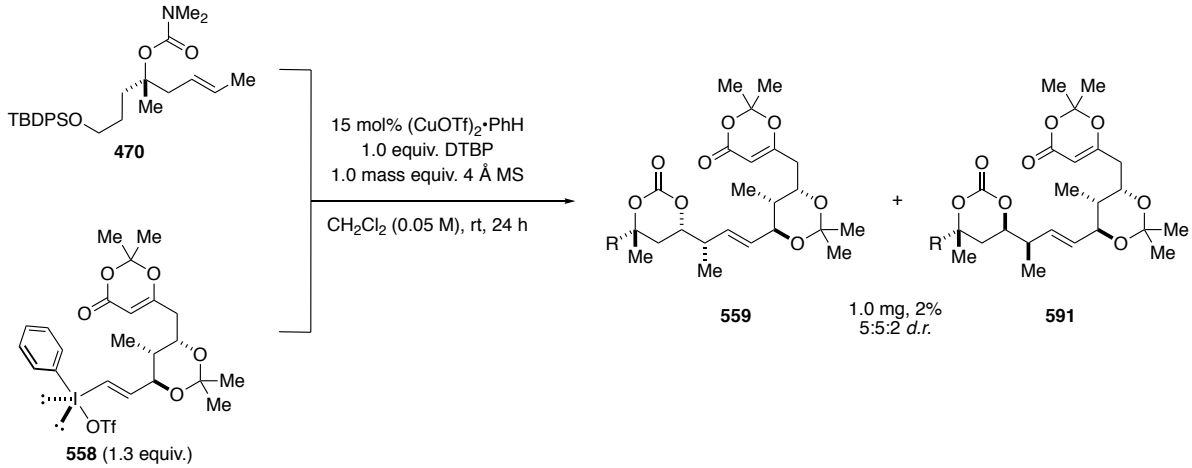
The low diastereoselectivity of the *oxy*-alkenylation process (2:2:1, **589**:**590**:other) was attributed to the tertiary alcohol-appended carbamate substrate. With the presence of a tertiary centre, it was considered that the putative transition states leading to the two suspected major isomers would differ only with respect to the steric demands of an axial methyl group compared with an axial methylene group (Scheme 131). Consistent with the similar A-values of a methyl and an ethyl group (1.70 *vs.* 1.75),[214] there appears to be little energetic preference for either transitions state structure and hence no appreciable diastereoselectivity.



Scheme 131 – Proposed origin of poor *oxy*-alkenylation diastereoselectivity

However, as the model reaction proceeded with no apparent decomposition of the carbamate substrate, the same conditions were applied to a fragment union reaction using our northern fragment iodonium salt **558** (Scheme 132). Pleasingly, evaluation of the crude reaction mixture by ^{1}H NMR and LCMS

indicated the presence of trace amounts of the desired product. Extensive chromatographic purification allowed the isolation of 1 mg (2%) of a species observed to bear ^{1}H signals and COSY cross-peaks consistent with coupled product **559** (Figure 13). The assignment was further supported by high resolution mass spectrometry with the observation of a diagnostic $[M+Na]^+$ signal. However, consistent with the model reactions performed by Dominik Reich, the NMR data indicated the coupled polyketide backbone to be formed in a low *d.r.* of 5:5:2 (**559**:**591**:other).



Scheme 132 – Coupling of southern fragment **470** and northern fragment **558** to furnish linear polyketide backbone **559**

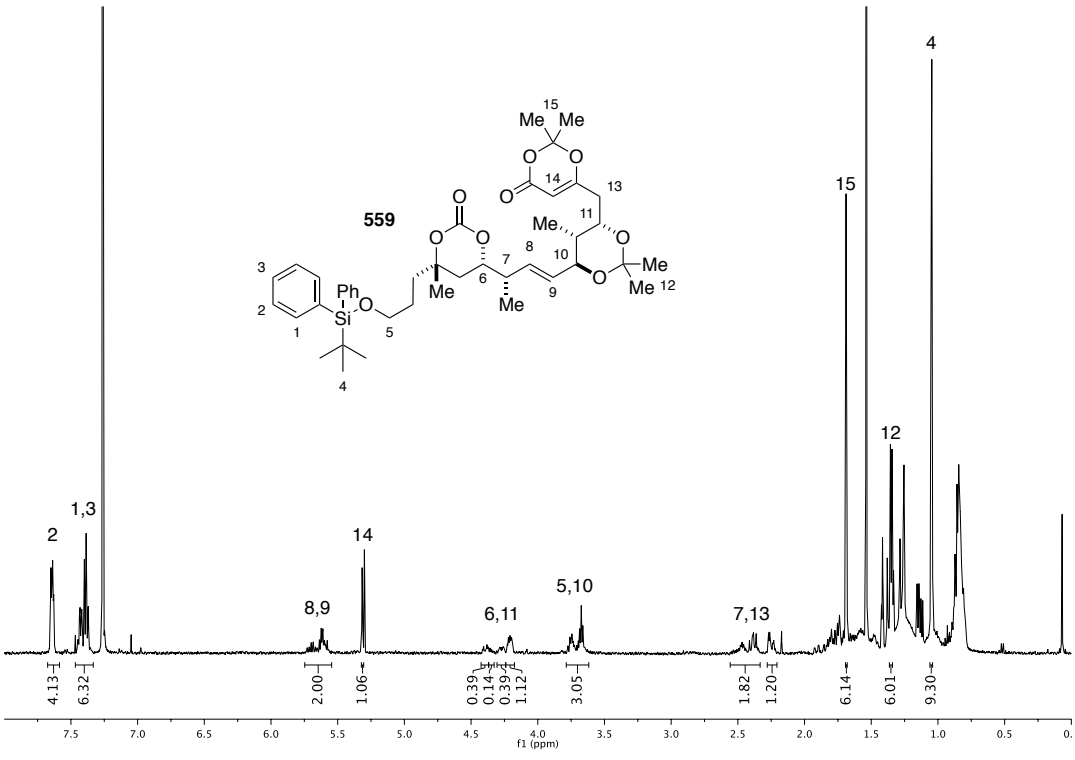


Figure 13 – ^{1}H spectrum of linear polyketide backbone **559** (500 MHz)

Whilst the above reaction was low yielding and poorly diastereoselective, this study indicates that our *oxy*-alkenylation methodology may be used as a fragment union strategy in polyketide synthesis. It is hoped that our approach will be pursued further in the future to produce (–)-lyngbyaloside B or other natural products.

3.8 Summary

This project has described investigations into the application of Gaunt's *oxy*-alkenylation strategy to the synthesis of the macrolide (–)-lyngbyaloside B. Efforts were directed toward the use of this reaction as a novel fragment union for polyketide synthesis. As such, this chapter has detailed studies into model fragment couplings, the synthesis of a highly complex polyoxygenated iodonium salt and the coupling of this fragment to an elaborate homoallylic carbamate substrate.

It has been demonstrated that protected, secondary, α-oxygenated alkenyl iodonium salts can be generated and isolated in moderate yields. Similarly, it was observed that model reactions for the desired fragment coupling proceed in synthetically useful yields. It was noted that the temperature of the reaction and steric parameters of the iodonium salt are important factors in controlling carbamate conversion and product stability. Furthermore, it was shown that an iodonium salt bearing a protected 1,3-diol with three contiguous stereocentres can be transferred to a simple homoallylic carbamate.

It was discovered that the choice of alcohol protecting group is very important in the synthesis of complex iodonium salts. Such elaborate iodanes were generally observed to be unstable to both acid and base, cyclising and eliminating under these conditions respectively. Finally, it was determined that acetonide protection was suitable for the generation and isolation of northern fragment iodonium salt **558**.

Following extensive investigations, the desired *oxy*-alkenylative fragment coupling was achieved in 2% yield and in 5:5:2 *d.r.*. Although the result of this reaction is not synthetically useful, it does evidence that the coupling of polyketide fragments using our methodology is possible.

4 Towards a Mechanistic Understanding of Copper-Catalysed Alkene Functionalisation with Diaryliodonium Salts

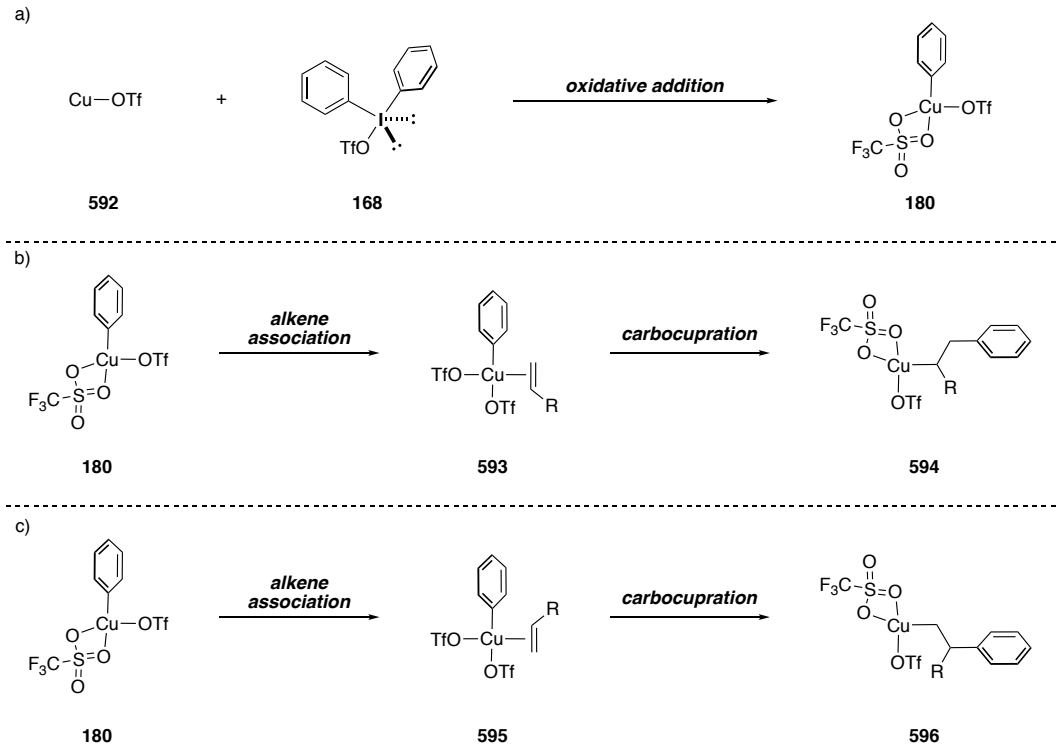
4.1 Project Overview

This project details very preliminary studies towards the computational evaluation of copper-catalysed alkene functionalisation processes. The reactivity of styrene with copper(I) triflate and diphenyliodonium triflate was first investigated, focusing on the distinct oxidative addition and alkene functionalisation steps of the reaction mechanism. It was demonstrated that the generation of a key copper(III) intermediate was thermodynamically favoured under the computed conditions and could proceed with only a small energetic barrier. Two accessible reaction modes have been determined for the functionalisation of styrene with the key Cu(III) intermediate. Subsequent work applied these insights towards the reaction of allylic amides under copper-catalysed arylation conditions and gave tentative results regarding the accessibility of regioisomeric reaction mechanisms.

4.2 Simple Alkene Functionalisation

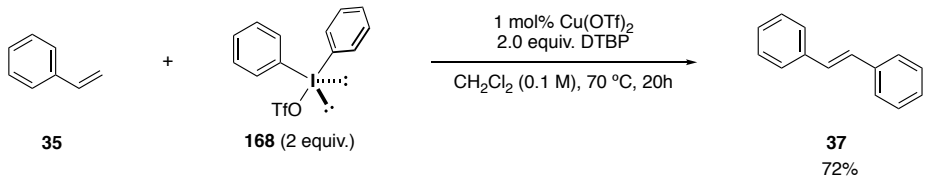
Despite the recent interest in copper-catalysed alkene functionalisation reactions using diaryliodonium salts, no mechanistic investigations into such processes have been reported in the literature. Although most of the transformations in this class appear to display carbocationic behaviour (see Section 1.5.5), exceptions to such reactivity are apparent, most notably the enamide generation procedure detailed in Chapter 2.[174] The reactivity of these alkene functionalisation processes is therefore clearly more complex than simply acting as a method to generate carbocations at the most stabilising centre. Disappointingly, all mechanistic investigations carried out within the Gaunt group towards understanding our copper-catalysed processes have so far given few results. The lack of insight gained can be attributed to the high reactivity of the copper-centred species, making sampling processes intrinsically difficult and the crystallisation of on-cycle intermediates problematic. With such challenges, computational studies were considered to be the best method for investigating the reactivity of copper-catalysed alkene functionalisation reactions using diaryliodonium salts.

At the outset of our computational investigations, it was thought that the reactivity observed in previous studies was best rationalised though carbocupration of the alkene substrate with a transiently-generated Cu(III)–aryl intermediate (Scheme 133). Such an alkene functionalisation process would give alkyl-copper(III) intermediates (*e.g.* **594** and **596**), able to undergo carbocation-like behaviour due to the extreme polarisation of the Cu(III)–alkyl bond. Variation in the regioselectivity of the carbocupration process would allow for the formation of both alkene arylation regioisomers. As such, efforts were directed towards understanding both the generation of a copper(III)–aryl intermediate and the ability of this species to undergo carbocupration with alkenes.



Scheme 133 – Proposed a) oxidative addition to furnish aryl–Cu(III) intermediate; b) alkene association and carbocupration to give more substituted carbocation-like intermediate; c) alkene insertion to give less substituted carbocation-like intermediate

The arylation of styrene **35** with diphenyliodonium triflate **168** was chosen as the model system for our preliminary studies (Scheme 134).[155] As is shown above, the mechanism of the reaction may be split into two distinct sections: oxidative addition (Scheme 133a) and alkene functionalisation (Schemes 133b and c). As it was anticipated that the oxidative addition process would be general across copper-catalysed carbofunctionalisation methods employing diaryliodonium salts, the individual sections of the reaction were investigated independently.

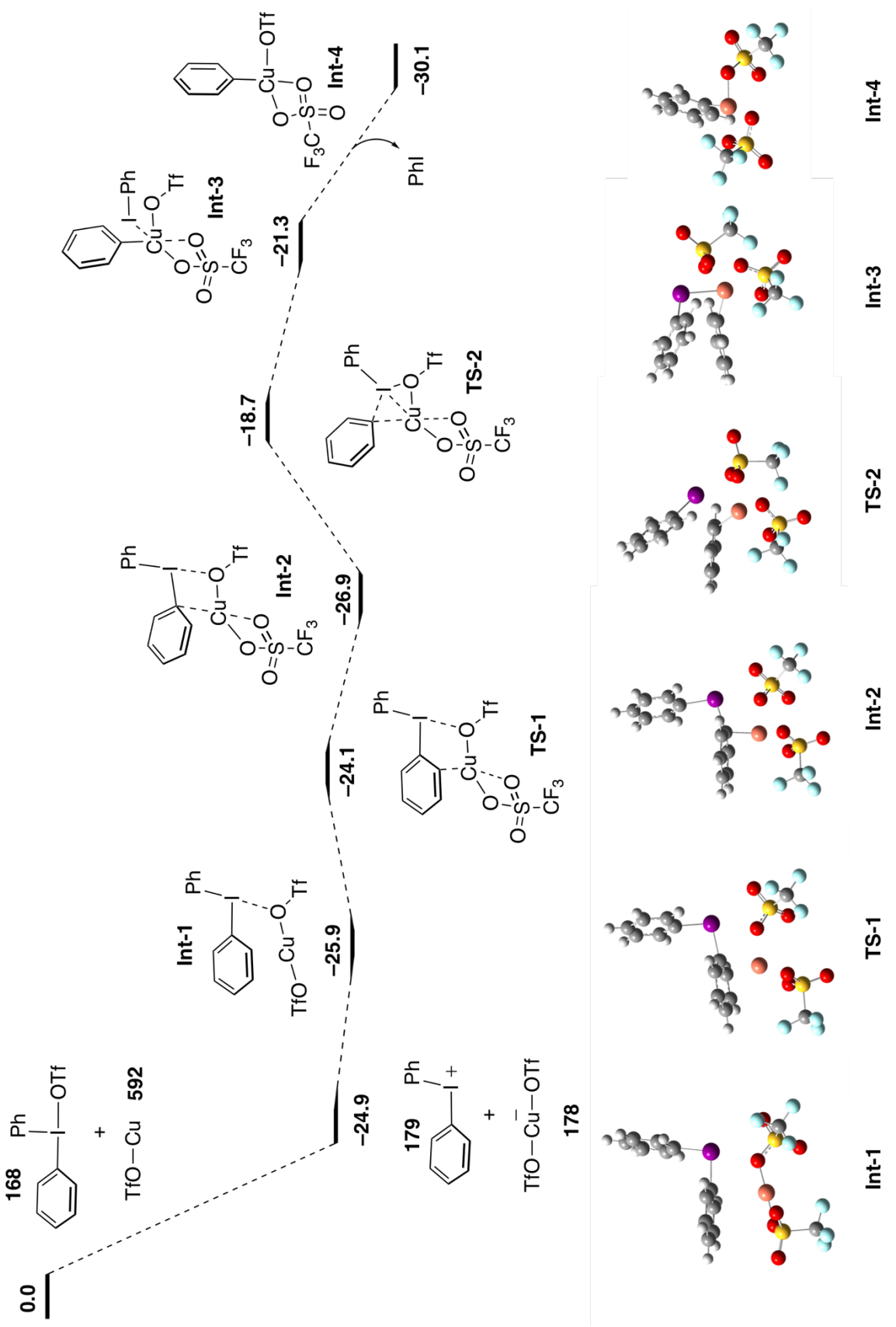


Scheme 134 – Gaunt's copper-catalysed styrene arylation giving stilbene **37**[155]

4.2.1. Oxidative addition

In line with work described by Lockhart, it is proposed that the active copper(I) triflate catalyst is produced from the copper(II) pre-catalyst by an *in situ* reduction (not shown).[98] The benchmarked calculation methods and basis sets used in Sanford's copper-catalysed fluorination reaction (Scheme 29, page 22)[101,102] were then applied to the system under investigation to allow an energy profile for the

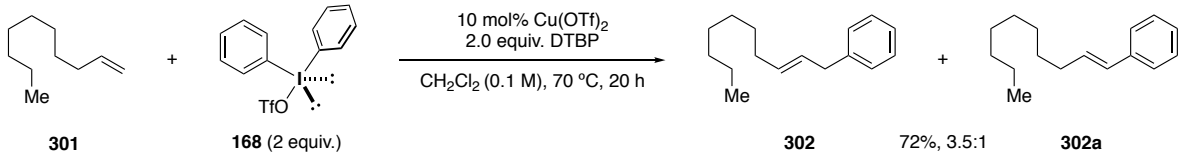
oxidative addition of copper(I) triflate **592** with diphenyliodonium triflate **168** to be elaborated (Scheme 135). It was initially computed that the transfer of a triflate ion from the iodonium salt to the neutral copper(I) species was energetically favourable, giving anionic copper(I) species **178** and diaryliodonium cation **179**. The charge-separated species were then calculated to recombine to form adduct **Int-1**, with this intermediate then rearranging through transition state **TS-1** ($\Delta G^{\ddagger}$ = +1.8 kcal^{-1}) to the stable *ipso*-coordinated oxidative addition precursor **Int-2**. Oxidative addition was computed to occur through transition state **TS-2** ($\Delta G^{\ddagger}$ = +8.2 kcal mol^{-1}) to give square-based pyramidal Cu(III) adduct **Int-3**. Entropically favoured dissociation of iodobenzene generates the key κ^2-triflate stabilised copper(III) intermediate **Int-4** (**180**). Although the existence of lower energy pathways to key intermediate **Int-4** cannot be discounted, this study demonstrates that the generation of this key copper(III) intermediate is thermodynamically favourable and kinetically accessible.



Scheme 135 – Oxidative addition of copper(I) triflate **592** into diphenyliodonium triflate **168** (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu,I], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

4.2.2. Styrene coupling

Attention was next directed towards modelling the reactivity of styrene with high-valent copper intermediate **Int-4**. It was initially anticipated that the alkene coordination and migratory insertion steps would occur analogously to those processes described for the palladium-catalysed Heck reaction.[215] However, in contrast to the Heck reaction, it was predicted that the stilbene formation would occur by an E2-type process rather than by a β-hydride elimination. This hypothesis derives from the observed production of alkene products that do not lie in conjugation with the introduced arene (Scheme 136).[155] Such compounds are not consistent with the β-hydride elimination behaviour of palladium species with acylic alkene substrates.[216] Computational investigations therefore targeted a reaction profile involving two key transition states: a concerted carbocupration to transfer the aryl group (**597**) and an E2-type elimination to furnish the stilbene product (**598**) (Figure 14).



Scheme 136 – Gaunt's copper-catalysed arylation of alkene **301** to give non-conjugated product **302**[155]

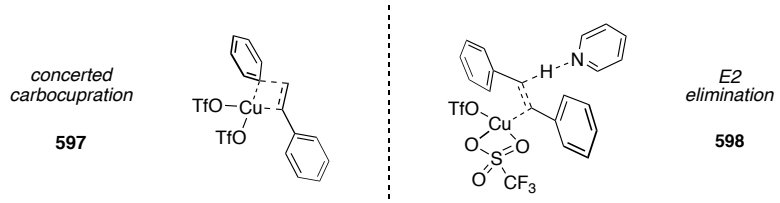


Figure 14 – Expected styrene functionalisation transition states

On introduction of styrene to the copper(III) intermediate **Int-4**, it was interesting to note that copper(III)-alkene adducts could only be identified with copper-alkene binding dominantly occurring through the alkene terminus. This binding mode differs from the expected Dewer-Chatt-Duncanson-type bonding where both alkene p-orbitals participate in the metal–alkene interaction.[28] An example of this interesting alkene-copper binding mode can be seen with **Int-5** (Figure 15). The observed unsymmetrical alkene binding can be rationalised through the electron-deficient copper centre acting to strongly polarise the bound alkene, formally placing a negative charge at the alkene terminus and building positive charge at the styrene benzylic position. Such extreme induced polarity is evidenced by the lengthened C=C bond and shortened C–Ph bond computed for the styrene in **Int-5** relative to the free alkene **35** (Figure 16, **Int-5**: 1.41 Å, 1.43 Å respectively; styrene: 1.35 Å, 1.47 Å).

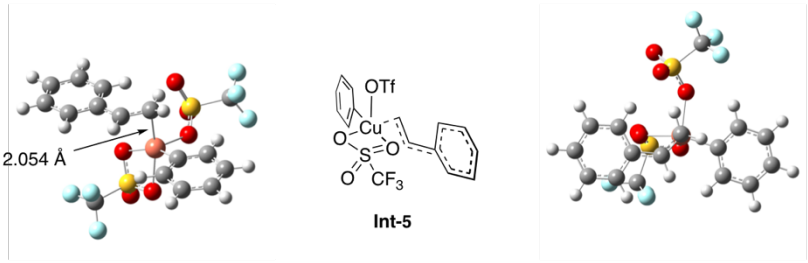


Figure 15 – Terminal π-bound styrene-Cu(III) complex **Int-5**

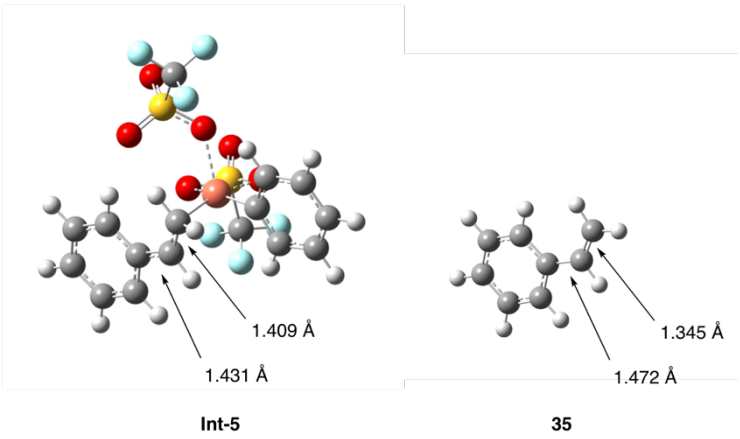


Figure 16 – Shortening of styrene C=C bond and lengthening of C–Ar bond on binding to **Int-5**

From **Int-5**, only one transition state (**TS-3**) was discovered that would lead towards the desired 1,2-substituted adduct ($\Delta G^{\ddagger}$ = +2.3 kcal mol^{-1}, Figure 17). Intriguingly, this transition structure appears to most closely resemble an early reductive elimination transition state.[217] Such reactivity can be rationalised by considering **Int-5** at its charge-separated resonance extreme **600**, bearing a formal alkyl-copper bond. Reductive elimination from such an anionic copper(III) centre reflects the computed behaviour (Scheme 137).

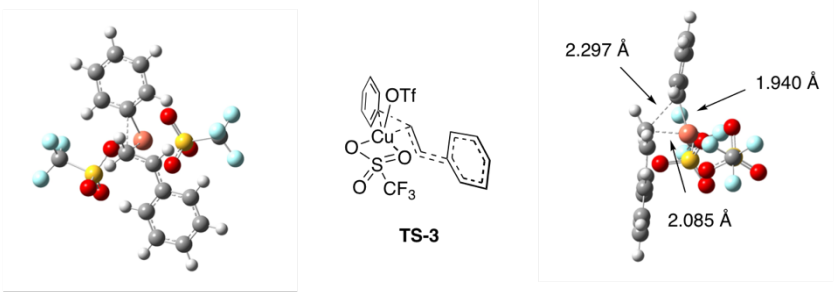
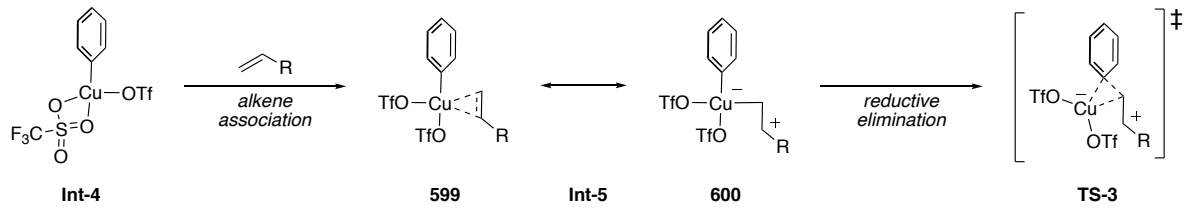
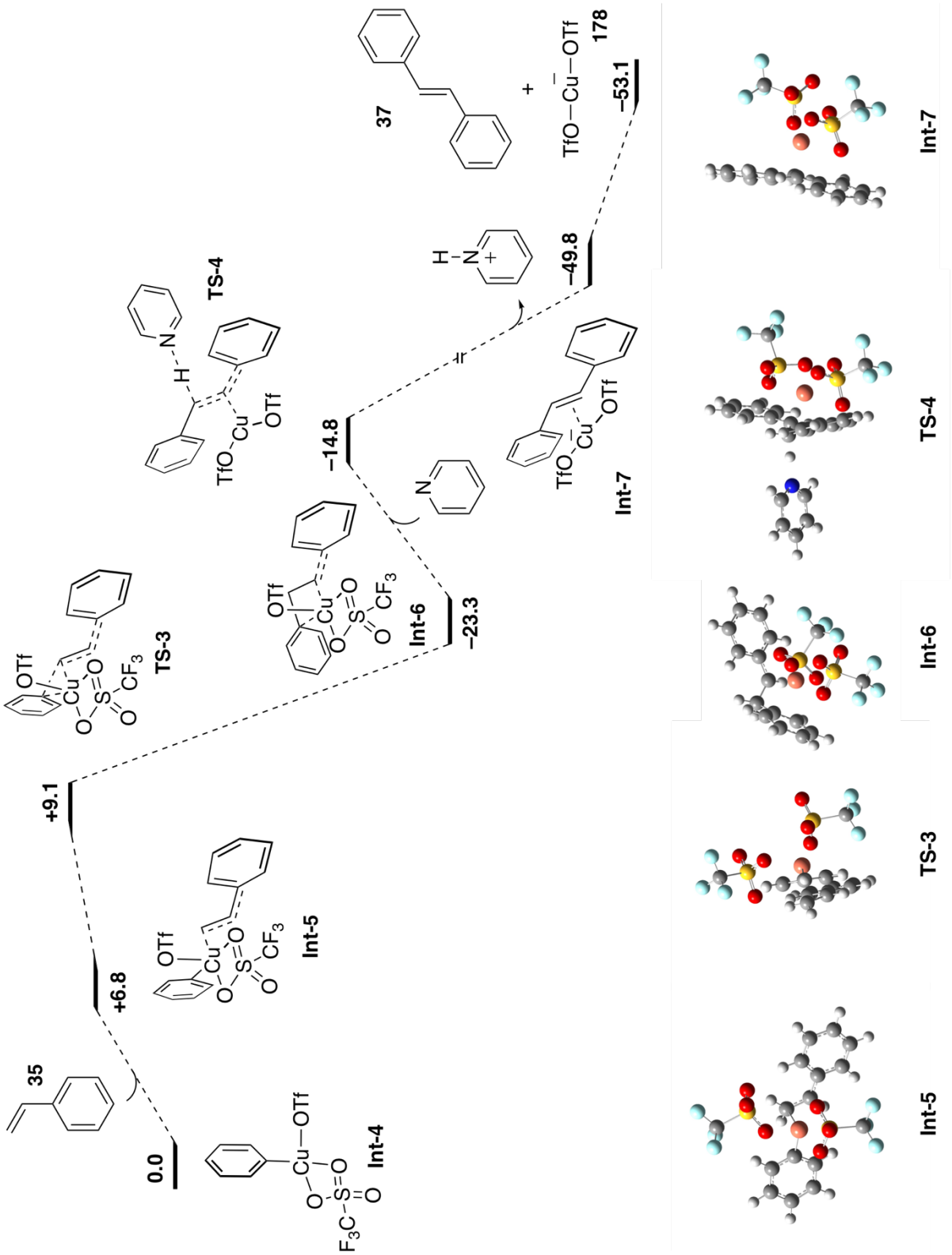


Figure 17 – Transition state leading to the desired stilbenium connectivity (**TS-3**)



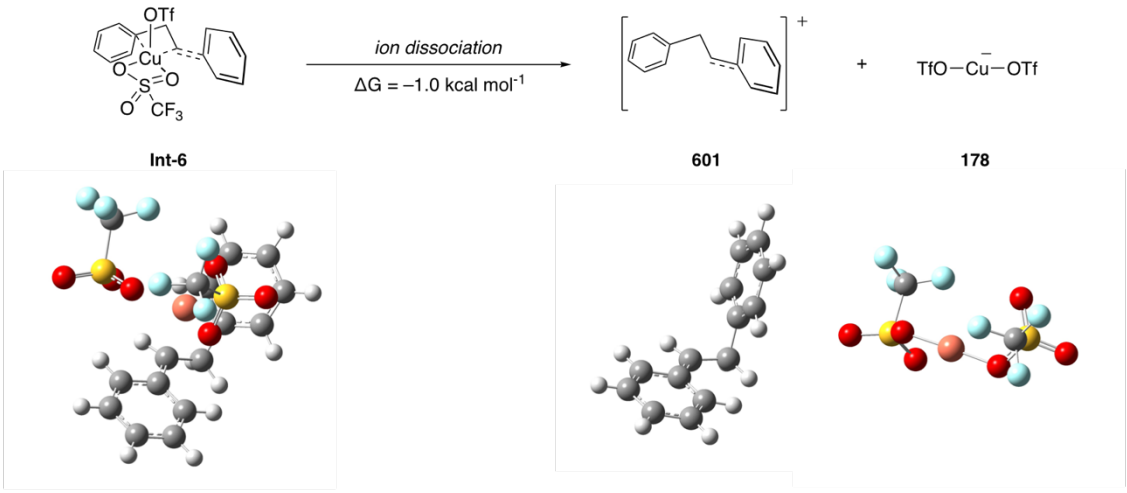
Scheme 137 – Rationale of alkene functionalisation through copper(III)-induced polarisation of alkene π-bond

With transition state **TS-3** in hand, work was carried out to elaborate a plausible functionalisation pathway towards the observed stilbene product (Scheme 138). It was calculated that styrene-bound adduct **Int-5** could be produced with only a slight energetic penalty on alkene association to the κ^2-stabilised copper(III) intermediate **Int-4** (ΔG = +6.8 kcal mol^{-1}). Subsequent aryl insertion occurs *via* computed transition state **TS-3** to furnish the aryl-coupled intermediate **Int-6** with a large associated gain in energy (ΔG = −30.1 kcal mol^{-1}). In line with our hypothesis, an E2 transition state (**TS-4**) was identified to lie 8.5 kcal mol^{-1} higher in energy than arylated intermediate adduct, providing exergonic access to stilbene-bound copper(I) triflate anion **Int-7**. Dissociation of the coupled stilbene product was computed to be thermodynamically favourable, allowing regeneration of the free anionic copper(I) triflate species **178**.



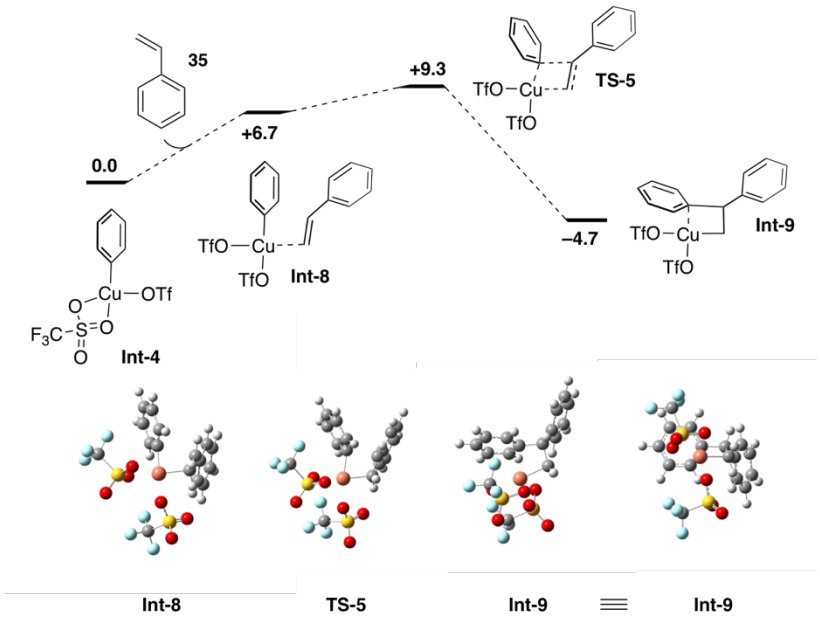
Scheme 138 – Association of styrene **35** to key κ^2-bound copper(III) species **Int-4** and reaction towards *trans*-stilbene production (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S,N]); energies given as ΔG (kcal mol^{-1})

Based on the observed reductive elimination-like chemistry of **TS-3**, it was considered that **Int-6** could alternatively be viewed as ionically-paired copper(I) anion-carbocation complex. Interestingly, the dissociation of **Int-6** into the free benzylic-stabilised carbocation **601** and copper(I) triflate anion **178** was determined to be favourable (Scheme 139, $\Delta G = -1.0$ kcal mol^{-1}). Importantly, this result implies that copper-catalysed alkene arylation can take place to give free carbocationic intermediates with the charge localised at the most stabilising position. This is consistent with many of the experimental observations described in the literature and allows rationalisation of elimination, fragmentation, isomerisation and hydride-shift processes (see Schemes 63 and 66, Section 1.5.5).[153,155,157]



Scheme 139 – Dissociation of **Int-6** to stilbenium ion **601** and copper(I) triflate anion **178** (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

However, the free carbocationic behaviour detailed above does not explain the potential for functionalisation at the non-nucleophilic position of alkene substrates.[174] Although no such reaction product is observed on the reaction of styrene with diaryliodonium salts under copper-catalysis, attention was turned towards further evaluating the reactivity of the copper(III)-styrene adduct. Mechanistic pathways were sought that would give functionalistion of the styrene with opposite regioselectivity to that described above. Interestingly, on re-orientating the bound alkene to give complex **Int-8**, a concerted carbocupration transition state (**TS-5**) could be identified leading to 1,1-disubstuted adduct **Int-9** (Scheme 140). It should be noted that this complex is calculated to have alkyl-copper bond length of 2.02 Å, considerably shorter than the computed analogous bond length for the 1,2-substituted adduct **Int-6** (2.16 Å). The relative difference in bond length implies a stronger copper-carbon interaction for the 1,1-insertion intermediate, indicative of a true copper(III) intermediate. Intriguingly, the transition state for this carbocupration process lies only very slightly higher in energy than the transition state calculated to give the stilbene product (**TS-5** *vs.* **TS-3**, $\Delta\Delta G^{\ddagger} = +0.2$ kcal mol^{-1}). This result implies the kinetic accessibility of two transition states giving regioisomeric products, offering a potential explanation for observed regiodivergence in the functionalisation of allylic amides.[174]



Scheme 140 – Association of styrene **35** to key κ²-bound copper(III) species **Int-4** and reactions towards 1,1-diphenylethylene production (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

It is anticipated that elimination processes from **Int-9** will be unfavourable due to the energetic penalty of losing the stabilising co-ordination of the aryl group. Such an energy barrier allows the absence of 1,1-diphenylethylene in the crude reaction mixture to be rationalised. Furthermore, given the relatively high energy of arylated intermediate **Int-9**, it is possible that the carbocupration process proceeding through **TS-5** will be reversible. Finally, an alternative explanation for the absence of 1,1-diphenylethylene in the reaction mixture would be the occurrence of a 1,2-aryl migration from **Int-9** to give the more stable **Int-6**, thereby ultimately giving stilbene formation.

4.2.3. Summary

Whilst further work is required to more fully understand the copper-catalysed arylation of alkenes with diaryliodonium salts, the investigations described in the above sections have given insight into the functionalisation modes that alkenes may undergo in the presence of high-valent copper intermediates. Tentatively, it can be concluded that at least two energetically accessible alkene functionalisation processes exist under such a reaction manifold. These two computed arylation modes resemble a reductive-elimination-like process (**TS-3**, Figure 18a) and a concerted carbocupration process (**TS-5**, Figure 18b) respectively and proceed to give regiosiomeric reaction products.

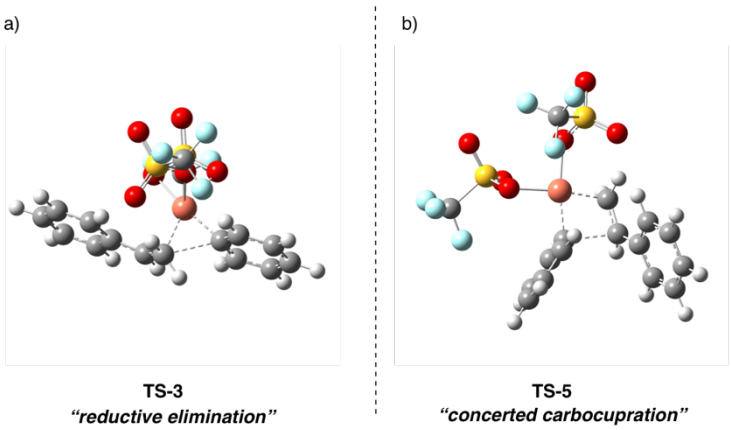
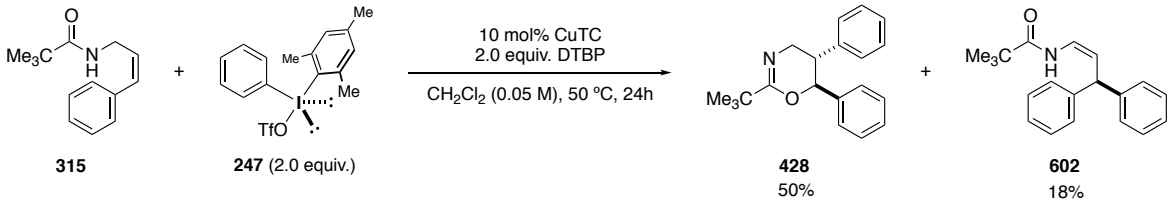


Figure 18 – Computed styrene functionalisation transitions states

4.3 Regiodivergent Arylation of Allylic Amides

The regiodivergent arylation mechanisms computed for the reactivity of styrene were next applied to the allylic amide arylation process investigated in chapter 2. Initial efforts were directed towards rationalising the outcome of a simple racemic model reaction shown to give both enamide and oxazine products (Scheme 141). As more oxazine product is observed in the crude reaction, it was anticipated that the transition state leading to oxazine formation would be slightly lower in energy than that giving enamide formation ($\Delta\Delta G^{\ddagger}$ 0–1 kcal mol^{-1}).



Scheme 141 – Racemic regiodivergent allylic amide arylation to furnish oxazine **428** and enamide **602** (NMR yields with 1,3,5-trimethoxybenzenetricarboxylate)

The functionalisation of the allylic amide towards oxazine **428** was first evaluated. In analogy with the computed reaction of styrene to give stilbene formation, alkene-binding adducts resembling the key styrene-bound intermediate **Int-5** were sought. Given the coordinating nature of the allylic amide carbonyl group, calculations were directed towards the generation of bidentate adducts. Cationic copper(III) complex **Int-10** was identified to fit these constraints (Figure 19).

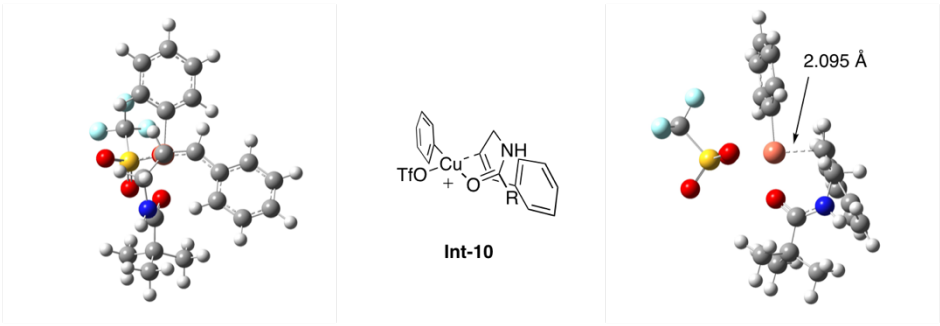
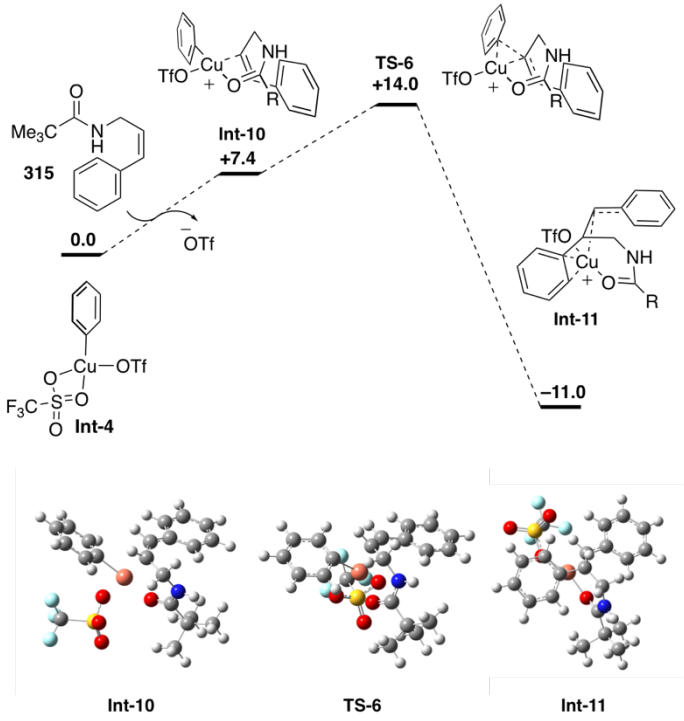
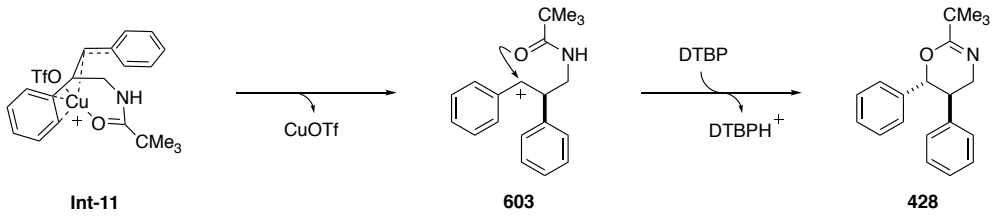


Figure 19 – Computed bidentate cationic allylic amide-bound copper(III) adduct **Int-10**

With **Int-10** in hand, an energy profile for reductive-elimination-like substrate arylation towards oxazine formation was generated to ultimately give arylated allylic amide complex **Int-11** (Scheme 142). These investigations indicated arylation of the substrate by this mechanism to be energetically accessible, though significantly higher in energy than the comparative styrene functionalisation (**TS-6** *vs.* **TS-3**: $\Delta G^{\ddagger}$ = 9.1 kcal mol^{-1} *vs.* 14.0 kcal mol^{-1}). It is proposed that arylated intermediate **Int-11** may be converted to the oxazine product through carbocation dissociation and carbonyl trapping (Scheme 143).



Scheme 142 – Reaction of amide **315** with **Int-4** towards oxazine formation (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})



Scheme 143 – Proposed generation of oxazine **428** from copper-bound intermediate **Int-11**

Interestingly, there appears to be a close resemblance between the transition state leading to oxazine formation and that leading to the production of stilbene (Figure 20). The styrene functionalisation appears to be stabilised by a hydrogen-bonding interaction from the alkene to a triflate ligand, placing a triflate oxygen where the carbonyl appears to bind to the copper centre for allylic amide arylation.

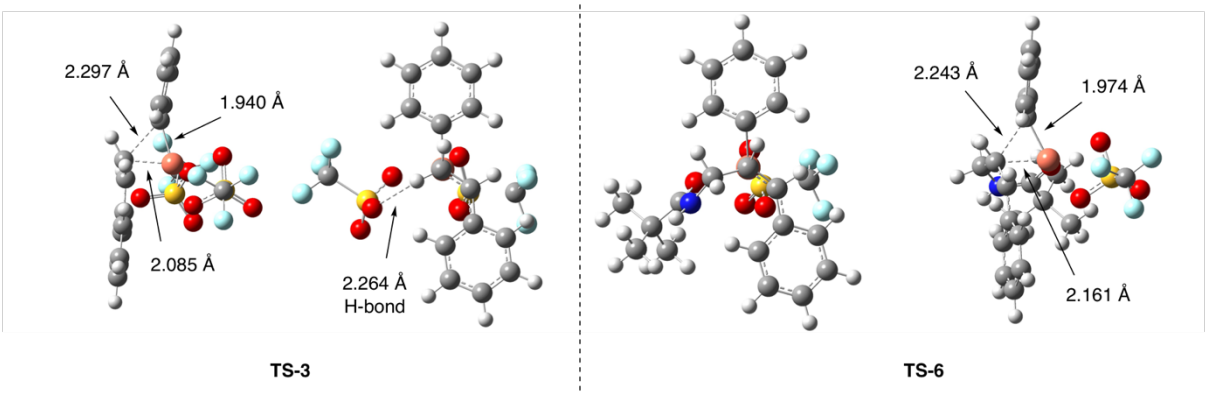
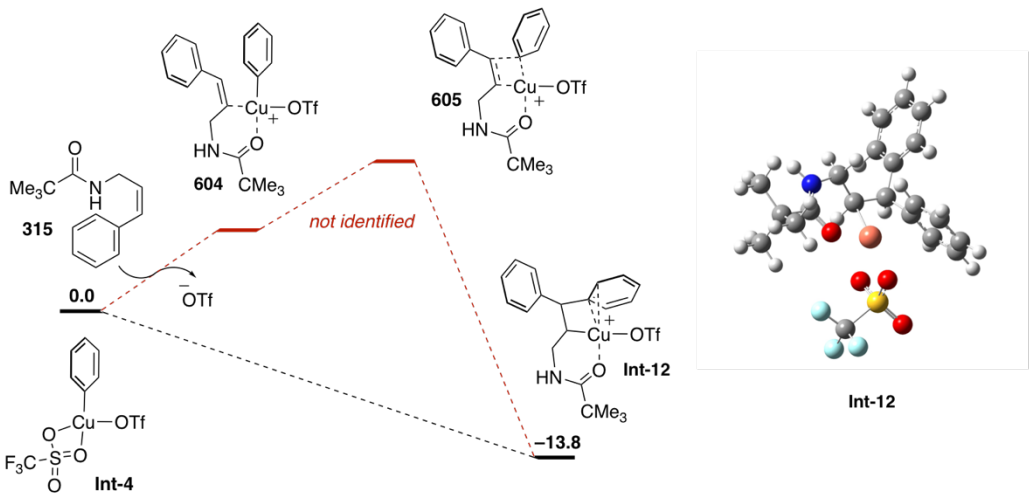


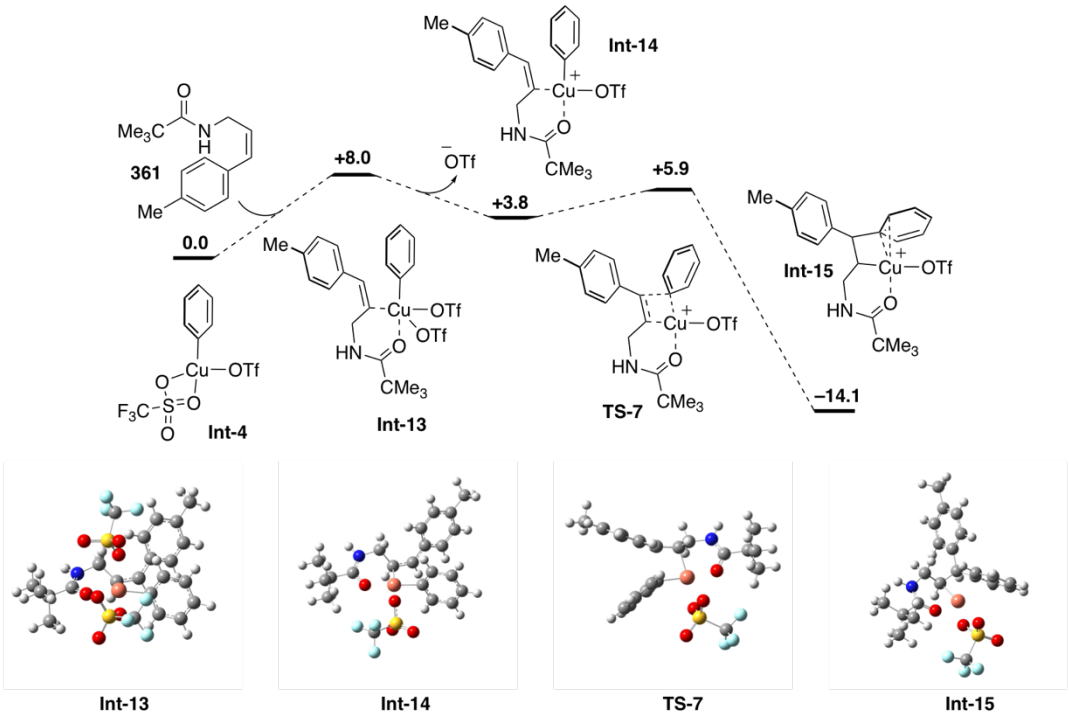
Figure 20 – Isostructural arylation transition states with styrene and allylic amide **315** respectively

Attention was next directed towards the identification of a concerted carbocupration transition state leading to enamide formation. Surprisingly, all efforts to coordinate the allylic amide to the copper centre in the expected reactive conformation led directly to the production of insertion intermediate **Int-12**. Interestingly, this species is observed to be lower in energy than the comparable intermediate leading to oxazine formation (**Int-11**), thereby implying a thermodynamic preference for enamide generation. No intermediate alkene-bound complex (**604**) or carbocupration transition state (**605**) could be identified on path towards the formation of **Int-12** (Scheme 144).



Scheme 144 – Reaction of amide **315** with **Int-4** towards enamide formation (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

An enamide-formation energy profile with identifiable intermediate adducts was computed for a different substrate using a more rigorous basis set (Scheme 145). It was revealed that cationic bidentate allylic amide copper(III) adduct **Int-14** is more stable than the neutral bistriflated species **Int-13**. Interestingly, the carbocupration transition state (**TS-7**) leading to enamide formation was calculated to lie just 2.1 kcal mol^{-1} higher in energy than **Int-14**. The low calculated activation energy explains the difficulty encountered for the convergence of alkene-bound intermediates in the above study.



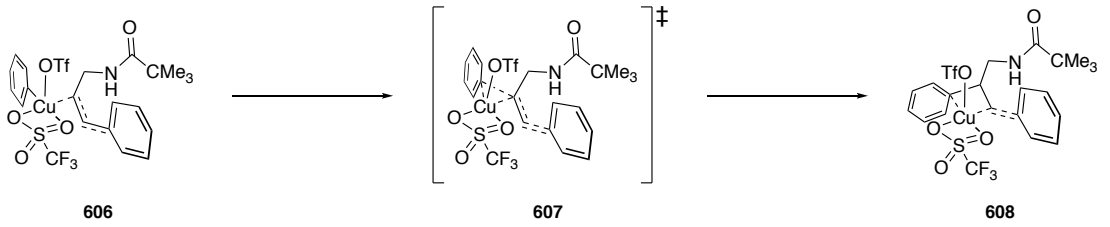
Scheme 145 – Reactivity of amide **361** with **Int-4** towards enamide formation (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Disappointingly, a transition state analogous to **TS-6** (oxazine formation, Scheme 142) could not be converged at the desired level of theory with *para*-tolyl substrate **361**. As such, no direct comparisons between the reaction profiles leading to oxazine and enamide generation can be made. However, it appears that the concerted carbocupration process giving enamide formation is remarkably facile, whilst the energetic profile calculated towards oxazine production appears too high in energy to be competitive (Scheme 142). It is therefore anticipated that a lower-energy process giving oxazine formation must exist on the potential-energy surface for the copper-catalysed arylation of allylic amides with diaryliodonium salts.

4.3.1. Future calculations

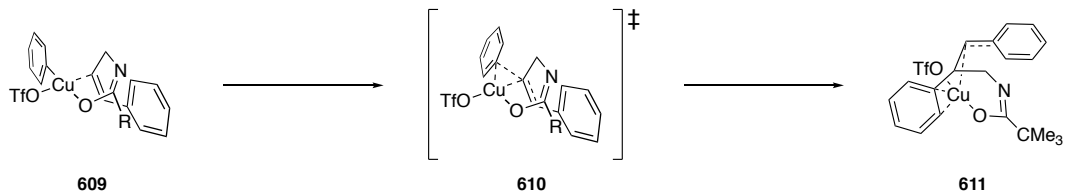
Owing to time limitations, no further work could be carried out to improve our understanding of the origins of the observed regiodivergence. It is hoped that further investigations in this area will be pursued in the future. In this eventuality, work should be first directed towards computing two other potential reaction pathways for oxazine formation:

Firstly, in direct analogy with the styrene functionalisation process, the reaction of allylic amide **315** with the key phenyl-Cu(III) electrophile **Int-4** should be computed with monodentate alkene binding (Scheme 146). As is discussed in Section 2.9, reaction through such a mechanism would allow for the rationalisation of oxazine selectivity with electron-rich iodonium salts



Scheme 146 – Possible monodentate allylic amide functionalisation mechanism towards oxazine formation

Secondly, the computations detailed in Scheme 142 should be re-computed with the amide deprotonated. It is anticipated that this change would give increased charge donation to the copper centre, stabilising the reductive elimination-like transition state (Scheme 147).



Scheme 147 – Formally anionic allylic amide functionalisation towards oxazine formation

Following the identification of a low-energy alkene functionalisation pathway giving oxazine formation, the effect of changing the aryl-group electronics should be investigated. It is anticipated that more

electron-rich aryl groups will alter the energies of the alkene functionalisation transition states to bias oxazine formation. Contrastingly, it is expected that more electron-poor aryl groups will relatively lower the energy of the carbocupration transition state, thereby favouring enamide formation.

4.4 Summary

Although the studies detailed in this section are incomplete, some important insights have been gained into the behaviour of copper-catalysed alkene functionalisation processes using iodonium salts. Firstly, it has been evidenced that little energy input is required to generate copper(III) intermediates from the combination of copper(I) species and iodonium salts. Furthermore, these copper(III) adducts have so far been computationally demonstrated to react with alkenes by two mechanisms, consistent with behaviour that has been observed experimentally. One such process resembles reductive elimination, directly coupling the aryl group from the iodonium salt to the more nucleophilic alkene position. The second reactivity mode appears as a concerted carbocupration – transferring the aryl group to the less intrinsically nucleophilic position of the alkene. The former process has been demonstrated to allow the formation of free carbocations in the reaction mixture, whilst the latter pathway permits rationalisation of the functionalisation of the non-nucleophilic alkene position. Further work is required to more fully understand and apply the behaviour of these systems.

5 Conclusion and Outlook

This thesis has described three projects related to the development, application and understanding of copper-catalysed alkene functionalisation processes using iodonium salts.

Chapter 2 details the development of a regiodivergent and enantioselective allylic amide arylation procedure. It was observed that the combination of diaryliodonium hexafluorophosphates and a specific copper(II)-bisoxazoline pre-catalyst allowed highly enantioselective alkene arylation to give enamide and oxazine products. The product distribution is controlled by the electronic properties of the diaryliodonium salt employed, wherein electron-rich aryl groups give oxazine production and electron-deficient arenes provide enamides. The reaction was shown to proceed using a variety of substrates and a number of diaryliodonium salts to provide a range of both products in high *e.e.* and synthetically-useful yields. It was further demonstrated that the enamide products may be converted to enantioentiched β,β'-diarylaldehydes, providing an umpolung strategy for the generation of these useful compounds.

Chapter 3 describes efforts towards the application of a copper-catalysed *oxy*-alkenylation procedure to the production of the polyketide natural product (–)-lyngbyaloside B. It was proposed that Gaunt's copper-catalysed methodology could be employed as a fragment union in the total synthesis of the macrolidal target, coupling an elaborate homoallylic carbamate fragment and a complex polyoxygenated alkenyl(aryl)iodonium salt. Following extensive studies, it was discovered that an acetonide-derivative of the desired iodane could be prepared and isolated in good yields. Reaction of the iodonium fragment with the relevant homoallylic carbamate (prepared by Dominik Reich) allowed the production of the coupled complex carbonate in 2% yield and as a mixture of diastereoisomers. These studies provide evidence that Gaunt's copper-catalysed *oxy*-alkenylation reaction may be used for the synthesis of polyketide backbones, though further work is required to make this strategy synthetically viable.

Chapter 4 presents preliminary studies towards the computational evaluation of the copper-catalysed arylation of simple alkenes. In line with work reported in the literature, it is shown that copper(III)-aryl adducts may be readily accessed from the combination of copper(I) sources and diaryliodonium salts. The interaction of a high-valent copper intermediate with styrene was then studied. Copper(III)-alkene-binding is evidenced to be unsymmetrical, with association occurring exclusively through the most nucleophilic carbon centre of the alkene. Two energetically-similar transition states, where the aryl group is transferred from the copper to the alkene, were identified. Arylation was predicted to be possible at both positions of the double bond. It was computed that a reductive elimination-like process can occur at the more nucleophilic alkene position to give terminal arylation whilst a concerted carbocupration can proceed to give internal arylation. These functionalisation modes were noted to be consistent with the regiodivergent behaviour observed on the exposure of allylic amides to diaryliodonium salts in the presence of a copper catalyst (chapter 2). Initial efforts investigating arylation towards enamide and

oxazine production were carried out and indicated concerted carbocupration giving enamide formation to be accessible. Further studies are required to elaborate a comparable low-energy oxazine-formation pathway.

Although the combination of diaryl- and alkenyl(aryl)iodonium salts and copper catalysts has been demonstrated to be a powerful method for the functionalisation of alkenes, there is a clear need for more in-depth understanding into the workings of this reactive system. Future work should be directed towards further elaborating the tentative results obtained by computationally modelling the behaviour of alkenes with copper(III)-aryl species. Insights could lead to the development of ligands to improve existing copper-catalysed reactions (*e.g.* greater levels of *oxy*-alkenylation diastereoselectivity) and may allow the rational design of new synthetic processes.

6 Experimental

6.1 General Information

Solvents: Unless otherwise stated, all reaction solvents were dried by standard techniques and freshly distilled before use or purchased in anhydrous form and used directly. Diethyl ether and tetrahydrofuran were distilled from lithium aluminium hydride and calcium hydride; acetonitrile, toluene and dichloromethane were distilled from calcium hydride; 1,2-dichloroethane and 1,4-dioxane were purchased from Acros Organics. Ethanol was used as purchased from Fisher Scientific. HPLC grade *iso*-propanol and *n*-hexane were purchased from Fisher Scientific. For purification purposes, petroleum ether 40–60, hexanes, ethyl acetate, dichloromethane, acetone and toluene were distilled before use; diethyl ether was used as purchased from Sigma Aldrich, acetonitrile was used as purchased from Fisher Scientific.

Reagents: All reagents were purified by standard procedures or used as purchased at the highest commercial quality.[i] Copper(II) triflate was stored and transferred in a glove-box under an atmosphere of nitrogen. Bisoxazoline ligand (+)-2,2′-Isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline] was stored at −18 °C under a head-space of nitrogen and transferred in a glove-box under an atmosphere of nitrogen.

Reactions: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen and were monitored by TLC, LCMS, GCMS or ^{1}H NMR as appropriate.

Iodonium salts: All aryl(mesityl)iodonium hexafluorophosphate salts were synthesised from the corresponding triflate or tetrafluoroborate species according to the procedure given in section 2, were dried *in vacuo* for a minimum of 18 hours and were stored in a vacuum desiccator over P_4O_{10}.

Chromatography: All flash chromatography for the preparation of allylic amides and enamides was carried out using Merck 9385 Kieselgel 60 silica gel under a positive pressure of nitrogen. All flash chromatography for the preparation of oxazines was carried out using Merck aluminium oxide 90 standardized under a positive pressure of nitrogen. All flash chromatography employed towards the total synthesis of (−)-Lyngbyaloside B was carried out under compressed air. Thin layer chromatography was carried out on Merck Kieselgel 60 PF254 0.2 mm plates. Visualisation was accomplished using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or acidic potassium permanganate solutions as appropriate.

Data collection: ^{1}H NMR spectra were recorded on a Bruker DPX 400 or 500 spectrometer. ^{13}C NMR spectra were recorded at 100 or 125 MHz on the same machines. ^{19}F NMR spectra were recorded at 376 MHz on a Bruker DPX 400 spectrometer. Chemical shifts (δ) are quoted in parts per million (p.p.m.) relative to residual solvent ($CDCl_3$: δ = 7.26 p.p.m. for ^{1}H and δ = 77.16 p.p.m. for ^{13}C; d_6-DMSO: δ = 2.50 p.p.m. for ^{1}H and δ = 39.52 p.p.m. for ^{13}C; d_3-MeCN: δ = 1.94 p.p.m. for ^{1}H and δ =

[i] Armarego, W. L. F.; Perrin, D. D., *Purification of Laboratory Chemicals*, 5th Ed. Butterworth-Heinemann, **1996**.

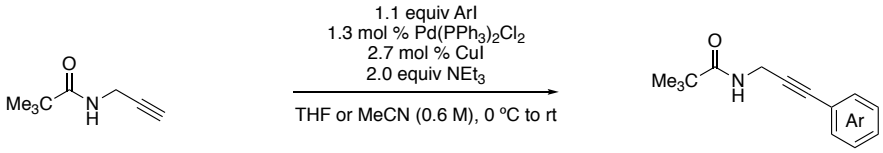
118.26 and 1.32 p.p.m. for ^{13}C; d_6-Me_2CO: δ = 2.05 p.p.m. for ^{1}H and δ = 206.26 and 29.84 p.p.m. for ^{13}C) to the nearest 0.1 p.p.m for ^{13}C and ^{19}F NMR spectroscopy and to the nearest 0.01 p.p.m for ^{1}H NMR spectroscopy. Coupling constants (J) are quoted to the nearest 0.1 Hz and are assumed to be J_{H-H} unless otherwise stated. Minor isotopes are given in squre brackets. The following abbreviations are used to indicate the form and multiplicity of the signals: s = singlet; d = doublet; t = triplet; q = quartet; qn = quintet; sx = sextet, sp = septet; m = multiplet; br. = broad; app. = apparent; and associated combinations, e.g. dd = doublet of doublets. Minor isotope couplings and partly obscured signals are indicated as such with square brackets. Mixtures of compounds are assigned individually where possible. The temperature of the acquisition of the NMR spectra was 298 ± 3K. DEPT135 and 2-dimensional experiments (COSY, HMBC, HSQC and NOESY) were used to support assignments where appropriate but are not included in this document. NMR yields were determined with trimethyl benzene-1,3,5-tricarboxylate, 1,2-dimethoxyethane or mesitylene as an internal standard. High-resolution mass spectra (HRMS) were measured either in the department or at the EPSRC Mass Spectrometry Service at the University of Swansea using electrospray ionisation (ESI), electron impact (EI) or atmospheric pressure solids analysis probe (ASAP) methods. Infared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer fitted with an ATR sampling accessory as either solids or neat films, either through direct application or deposited in chloroform or dichloromethane, with absorptions reported in wavenumbers (cm^{-1}). Optical rotations were measured in chloroform or acetone on a Perkin Elmer 343 Polarimeter using a sodium lamp (λ 589 nm, D-line). $[\alpha]_D$ values are reported at a given temperature (^oC) in 10^{-1} degrees cm^2 g^{-1} with concentration in mg mL^{-1}. Melting points (T_m) were recorded using a Gallenkamp hot stage apparatus and are reported uncorrected. Chiral HPLC analysis was performed on a Shimadzu XR-LC apparatus with chiralpak (IB, IC and AD-H) or chiralcel OD columns in a mixed solvent system of *n*-hexane and *iso*-propanol. Chiral GC-FID analysis was performed on a Shimadzu GC-2010+ apparatus with a chiraldex B-DM column with compressed air, hydrogen and helium as carrier gases. X-ray crystallography was performed on a Nonius Kappa CCD diffractometer or a Bruker D8-QUEST PHOTON-100 diffractometer using CuKa radiation (lambda = 1.5418 Å) at the Cambridge University Chemistry X-Ray Laboratory.

6.2 The Enantioselective and Regiodivergent Copper-Catalysed Arylation of Allylic Amides with Diaryliodonium Salts

6.2.1. General procedures

General procedure ***A***

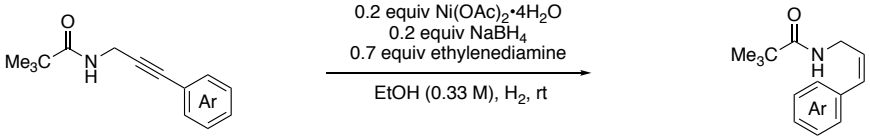
Preparation of Sonogoshira coupled alkynes:



Dry triethylamine (2.0 equiv) was added slowly at 0 °C to a stirred solution/suspension of propargylic alkyne (1.0 equiv, 0.60 M), aryl iodide (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (1.3 mol%) and CuI (2.7 mol%) in either dry tetrahydrofuran or acetonitrile. The reaction mixture was warmed to room temperature and was stirred for the stated time. The resulting solution/suspension was concentrated *in vacuo* and the residue dissolved in ethyl acetate, washed with water and brine, then dried over anhydrous $MgSO_4$. The filtrate was concentrated *in vacuo* and the residue purified by silica column chromatography to furnish the desired aryl-coupled product.

General procedure ***B***

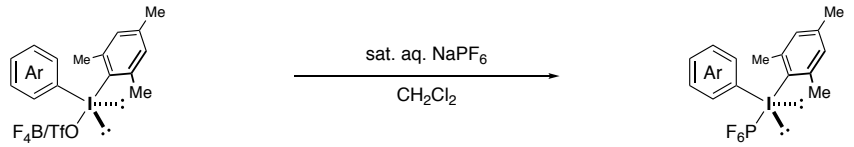
Preparation of allylic amide substrates:



Adapted from a procedure reported by Suffert et al.[218] $NaBH_4$ (0.2 equiv, 1 M in abs. ethanol) was introduced to a stirred suspension of $Ni(OAc)_2$•$4H_2O$ (0.2 equiv, 0.1 M in abs. ethanol) under an atmosphere of hydrogen gas. The resulting reductive mixture was stirred for a further two hours before undergoing the addition of a solution of ethylenediamine (0.7 equiv) and the alkyne (1.0 equiv, 1 M in abs. ethanol). This black suspension was then stirred for the given time under an atmosphere of hydrogen before being concentrated *in vacuo*. The resulting residue was suspended in ethyl acetate, then filtered through a plug of silica eluting with further quantities of ethyl acetate. This crude product solution was concentrated *in vacuo* and purified by silica column chromatography to furnish the desired allylic amide substrate.

General procedure ***C***

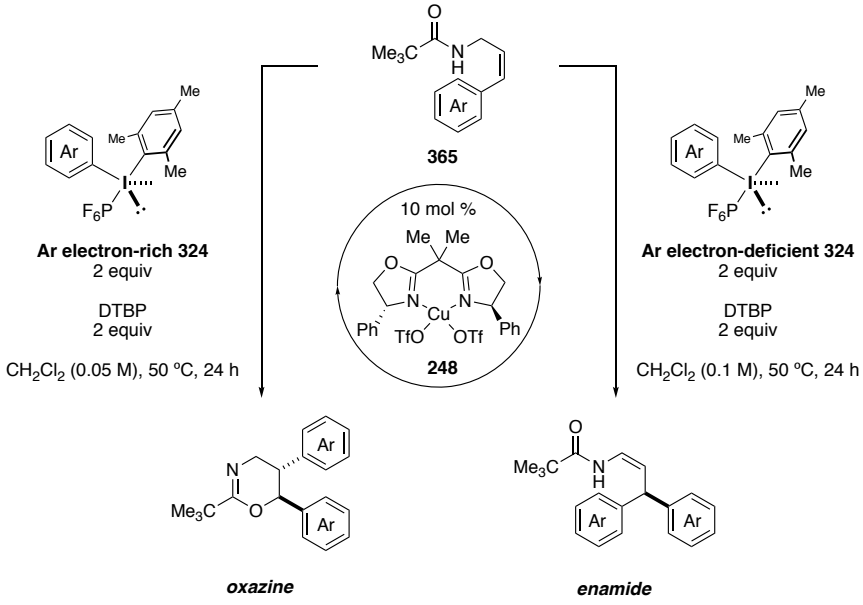
Production by diaryliodonium hexafluorophosphate salts by ion exchange:



An equal volume of a saturated aqueous solution of sodium hexafluorophosphate was added to a solution of aryl(mesityl)iodonium triflate/tetrafluroborate in dichloromethane (0.5 M). The resulting biphasic mixture was stirred at room temperature for the stated time before the phases were separated and the aqueous layer extracted with a further three portions of dichloromethane. The combined organic fractions were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the corresponding aryl(mesityl)iodonium hexafluorophosphate.

General Procedure ***D***

Regiodivergent copper-catalysed enantioselective allylic amide arylation:



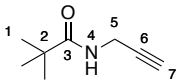
An oven-dried microwave tube was charged with the appropriate allylic amide (1.0 equiv) and diaryliodonium hexafluorophosphate (2.0 equiv), then sealed and back-filled with nitrogen gas. Dichloromethane was added *via* syringe, followed by the addition of 2,6-di-*tert*-butyl pyridine (DTBP, 2.0 equiv) and a pre-formed stock solution of **248**[ii] (10 mol%, unless otherwise stated). The resulting green solution (0.05–0.1 M *wrt* allylic amide loading) was heated at 50 °C for 24 hours (unless otherwise stated), cooled to room temperature and poured into an equal volume of sat. aq. $NaHCO_3$ solution. The phases were separated and the aqueous layer extracted with two portions of dichloromethane. The combined organic fractions were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and the crude residue purified by column chromatography to furnish the desired enantioenriched arylated product.

[ii] The stock solution of **248** is prepared as follows: in a glove-box under an inert atmosphere, an oven-dried microwave tube containing ~200 mg freshly activated 4 Å molecular sieves and a stirrer bar was charged with anhydrous $Cu(OTf)_2$ (72 mg, 0.2 mmol) and sealed. Subsequently, a solution of (+)-2,2-isopropylidenebis[(4R)-4-phenyl-2-oxazoline] ((+)PhBOX) (74 mg, 0.22 mmol) in dry dichloromethane (2 mL) was introduced to the anhydrous $Cu(OTf)_2$ and the resulting green solution stirred at room temperature for 15 hours. The resulting green solution was stored in the sealed tube under N_2 at -18 °C and used as required.

6.2.2. Substrate synthesis

6.2.2.1 Alkyne synthesis

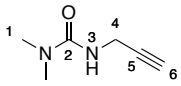
N-(prop-2-yn-1-yl)pivalamide **353**[157]



Dry triethylamine (34.0 mL, 241 mmol) was added dropwise at 0 °C to a solution of pivaloyl chloride (30.0 mL, 241 mmol) and propargylamine (14.0 mL, 219 mmol) in dichloromethane (340 mL). The resulting yellow suspension was warmed to room temperature and stirred for 15 hours before being quenched by the addition of sat. aqueous NH_4Cl solution (250 mL). The phases were separated and the aqueous layer washed with dichloromethane (2 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by silica flash column chromatography, eluting with 50% ethyl acetate in petroleum ether 40–60, to give the title compound as an off-white crystalline solid (30.0 g, 216 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81 (br. s, 1H, H-4), 4.04 (dd, $\mathcal{J}$ = 5.0, 2.5 Hz, 2H, H-5), 2.24 (t, $\mathcal{J}$ = 2.5 Hz, 1H, H-7), 1.21 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5 (C-3), 80.2 (C-6), 72.0 (C-7), 39.0 (C-2), 29.8 (C-5), 27.9 (C-1). Experimental data in agreement with previous literature report.[2]

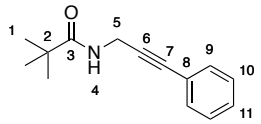
1,1-Dimethyl-3-(prop-2-yn-1-yl)urea **350a**



Dry triethylamine (7.10 mL, 51.0 mmol) was added dropwise at 0 °C to a solution of dimethylcarbamic chloride (4.70 mL, 51.0 mmol) and propargylamine (2.94 mL, 46.0 mmol) in dichloromethane (70 mL). The resulting yellow suspension was warmed to room temperature and stirred for 18 hours before being quenched by the addition of sat. aq. NH_4Cl solution (50 mL). The phases were separated and the aqueous layer extracted with dichloromethane (2 x 25 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by silica flash column chromatography, eluting with 5% methanol in dichloromethane, to give the title compound as an off-white crystalline solid (2.46 g, 19.5 mmol, 42%).

T_m 71–73 °C; IR ν_{max}/cm^{-1} (film): 3293 (br., N–H), 2925, 1631 (C=O), 1522, 1377, 1263, 1221; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.55 (br. s, 1H, H-3), 4.01 (dd, $\mathcal{J}$ = 5.3, 2.5 Hz, 2H, H-4), 2.90 (s, 6H, H-1), 2.20 (t, $\mathcal{J}$ = 2.5 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7 (C-2), 81.1 (C-5), 71.0 (C-6), 36.2 (C-1), 30.7 (C-4); HRMS-ESI (m/z) found $[M]^+$ 126.0786, $C_6H_{10}N_2O$ requires 126.0788.

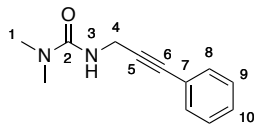
N-(3-phenylprop-2-yn-1-yl)pivalamide **315a** [157]



Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (3.88 g, 27.9 mmol), iodobenzene (3.43 mL, 30.7 mmol), $Pd(PPh_3)_2Cl_2$ (253 mg, 0.36 mmol) and CuI (143 mg, 0.75 mmol) in acetonitrile (45 mL) with stirring for 15 hours. Crude residue purified by silica column chromatography, eluting with 20 to 30% diethyl ether in petroleum ether 40–60 to furnish the title compound as a yellow solid (5.78 g, 26.8 mmol, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.42 (m, 2H, H-9), 7.32–7.30 (m, 3H, H-10,11), 5.89 (br. s, 1H, H-4), 4.28 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.24 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.3 (C-3), 132.1 (C-9), 128.8 (C-11), 128.6 (C-10), 122.9 (C-8), 85.4 (C-7), 83.8 (C-6), 39.0 (C-2), 30.6 (C-5), 27.8 (C-1). Experimental data in agreement with previous literature report.[157]

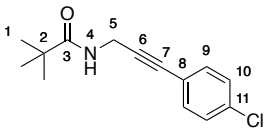
1,1-Dimethyl-3-(3-phenylprop-2-yn-1-yl)urea **350b**



Prepared according to general procedure **A** with *1,1-dimethyl-3-(prop-2-yn-1-yl)urea* **350a** (2.46 g, 19.5 mmol), iodobenzene (2.40 mL, 21.5 mmol), $Pd(PPh_3)_2Cl_2$ (177 mg, 0.25 mmol) and CuI (100 mg, 0.53 mmol) in acetonitrile (35 mL) with stirring for 48 hours. Crude product purified by silica flash column chromatography, eluting with 5% MeOH in dichloromethane, to yield the title compound as an orange crystalline solid (2.70 g, 13.3 mmol, 68%).

T_m 72–75 °C; IR ν_{max}/cm^{-1} (film): 3325 (br., N–H), 2928, 1638 (C=O), 1530, 1379, 1346, 1224; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.40 (m, 2H, H-8), 7.29–7.27 (m, 3H, H-9,10), 4.63 (br. s, 1H, H-3), 4.25 (d, $\mathcal{J}$ = 5.2 Hz, 2H, H-4), 2.92 (s, 6H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8 (C-2), 131.8 (C-8), 128.3 (C-10), 128.3 (C-9), 122.8 (C-7), 86.4 (C-6), 82.9 (C-5), 36.2 (C-1), 31.5 (C-4); HRMS-ESI (*m/z*) found $[M+H]^+$ 203.1177, $C_{12}H_{15}N_2O$ requires 203.1179.

N-(3-(4-chlorophenyl)prop-2-yn-1-yl)pivalamide **356a**

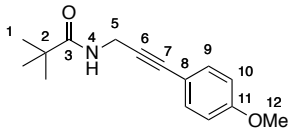


Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (1.01 g, 7.20 mmol), 4-chloroiodobenzene (1.91 g, 7.99 mmol), $Pd(PPh_3)_2Cl_2$ (65.8 mg, 93 μmol) and CuI (37.2 mg, 0.20 mmol) in acetonitrile (12 mL) with stirring for 18 hours. Crude residue purified by silica column

chromatography, eluting with 50% diethyl ether in petroleum ether 40–60 to furnish the title compound as a yellow crystalline solid (1.39 g, 5.50 mmol, 77%).

T_m 92–94 °C; IR ν_{max}/cm^{-1} (film): 3339 (br., N–H), 2966, 1644 (C=O), 1520, 1489, 1349, 1207, 1091, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, $\mathcal{J}$ = 8.6 Hz, 2H, H-9), 7.28 (d, $\mathcal{J}$ = 8.6 Hz, 2H, H-10), 5.83 (br. s, 1H, H-4), 4.26 (d, $\mathcal{J}$ = 5.1 Hz, 2H, H-5), 1.23 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2 (C-3), 134.7 (C-11), 133.1 (C-9), 128.8 (C-10), 121.2 (C-8), 86.2 (C-7), 82.4 (C-6), 38.9 (C-2), 30.3 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 250.0993, $C_{14}H_{17}NOCl$ requires 250.0993.

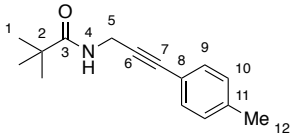
N-(3-(4-methoxyphenyl)prop-2-yn-1-yl)pivalamide **360a**



Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (1.01 g, 7.20 mmol), 4-iodoanisole (1.87 g, 7.99 mmol), $Pd(PPh_3)_2Cl_2$ (65.8 mg, 93 µmol) and CuI (37.2 mg, 0.20 mmol) in of acetonitrile (12 mL) with stirring for 14 hours. Crude residue purified by silica column chromatography, eluting with 50% diethyl ether in petroleum ether 40–60 to furnish the title compound as a white crystalline solid (1.52 g, 6.20 mmol, 86%).

T_m 58–60 °C; IR ν_{max}/cm^{-1} (film): 3331 (br., N–H), 2960, 2937, 1640 (C=O), 1606, 1508, 1289, 1246, 1205, 1172, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, $\mathcal{J}$ = 8.9 Hz, 2H, H-9), 6.83 (d, $\mathcal{J}$ = 8.9 Hz, 2H, H-10), 5.80 (br. s, 1H, H-4), 4.25 (d, $\mathcal{J}$ = 4.9 Hz, 2H, H-5), 3.81 (s, 3H, H-12), 1.23 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (C-3), 159.9 (C-11), 133.3 (C-9), 114.8 (C-8), 114.1 (C-10), 83.7 (C-7), 83.5 (C-6), 55.4 (C-12), 38.8 (C-2), 30.5 (C-5), 27.7 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 246.1489, $C_{15}H_{20}NO_2$ requires 246.1489.

N-(3-(p-tolyl)prop-2-yn-1-yl)pivalamide **361a**

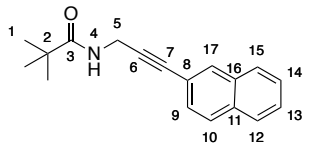


Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (2.99 g, 21.5 mmol), 4-iodotoluene (5.14 g, 23.6 mmol), $Pd(PPh_3)_2Cl_2$ (195 mg, 0.28 mmol) and CuI (110 mg, 0.58 mmol) in tetrahydrofuran (40 mL) with stirring for 4 hours. Crude residue purified by silica column chromatography, eluting with 5 to 20% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a white crystalline solid (3.55 g, 15.5 mmol, 72%).

T_m 90–92 °C; IR ν_{max}/cm^{-1} (film): 3340 (br., N–H), 2966, 1640 (C=O), 1509, 1480, 1351, 1205, 1007, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, $\mathcal{J}$ = 8.1 Hz, 2H, H-9), 7.11 (d, $\mathcal{J}$ = 8.1 Hz, 2H, H-10), 5.84 (br. s, 1H, H-4), 4.25 (d, $\mathcal{J}$ = 4.9 Hz, 2H, H-5), 2.34 (s, 3H, H-12), 1.22 (s, 9H, H-1); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 178.1 (C-3), 138.7 (C-11), 131.8 (C-9), 129.2 (C-10), 119.6 (C-8), 84.4 (C-7), 83.7 (C-6), 38.8 (C-2), 30.5 (C-5), 27.6 (C-1), 21.6 (C-12); HRMS-ESI (*m/z*) found $[M+H]^+$ 230.1539, $C_{15}H_{20}NO$ requires 230.1539.

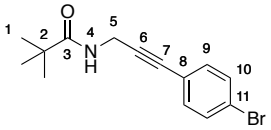
N-(3-(naphthalen-2-yl)prop-2-yn-1-yl)pivalamide **362a**



Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (834 mg, 6.00 mmol), 2-iodonapthalene (1.68 g, 6.60 mmol), $Pd(PPh_3)_2Cl_2$ (54.4 mg, 77 µmol) and CuI (30.7 mg, 0.16 mmol) in acetonitrile (10 mL) with stirring for 18 hours. Crude residue purified by silica column chromatography, eluting with 20 to 35% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a yellow crystalline solid (1.20 g, 4.90 mmol, 82%).

T_m 104–107 °C; IR ν_{max}/cm^{-1} (film): 3329 (br., N–H), 3056, 2968, 1637 (C=O), 1597, 1514, 1483, 1352, 1201, 817, 743; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.96 (s, 1H, H-17), 7.83–7.77 (m, 2H, H-13,14), 7.78 (d, $\mathcal{J}$ = 8.4 Hz, 1H, H-10), 7.51–7.48 (m, 2H, H-12,15), 7.47 (dd, $\mathcal{J}$ = 8.4, 1.6 Hz, 1H, H-9), 5.88 (br. s, 1H, H-4), 4.33 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.25 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.0 (C-3), 132.9 (C-11), 132.9 (C-16), 131.7 (C-17), 128.4 (C-9), 128.0 (C-10), 127.7 (2C, C-13,14), 126.7 (2C, C-12,15), 119.8 (C-8), 85.3 (C-7), 83.8 (C-6), 38.7 (C-2), 30.4 (C-5), 27.5 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 266.1542, $C_{18}H_{20}NO$ requires 266.1539.

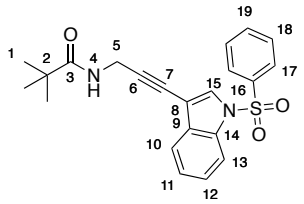
N-(3-(4-bromophenyl)prop-2-yn-1-yl)pivalamide **363a**



Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (1.01 g, 7.20 mmol), 4-bromoiodobenzene (2.26 g, 7.99 mmol), $Pd(PPh_3)_2Cl_2$ (65.8 mg, 93 µmol) and CuI (37.2 mg, 0.20 mmol) in acetonitrile (12 mL) with stirring for 18 hours. Crude residue purified by silica column chromatography, eluting with 50% diethyl ether in petroleum ether 40–60 to furnish the title compound as a yellow crystalline solid (1.71 g, 5.80 mmol, 81%).

T_m 108–110 °C; IR ν_{max}/cm^{-1} (film): 3338 (br., N–H), 2966, 1642 (C=O), 1518, 1485, 1349, 1292, 1259, 1206, 1071, 1011; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, $\mathcal{J}$ = 8.5, Hz, 2H, H-10), 7.27 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-9), 5.85 (br. s, 1H, H-4), 4.24 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.22 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2 (C-3), 133.3 (C-10), 131.7 (C-9), 122.8 (C-11), 121.7 (C-8), 86.4 (C-7), 82.5 (C-6), 38.8 (C-2), 30.3 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 294.0490, $C_{14}H_{17}NOBr$ requires 294.0488.

N-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)prop-2-yn-1-yl)pivalamide **364a**



To a solution of indole (2.00 g, 17.1 mmol) in dimethylformamide (30 mL) was added potassium hydroxide (2.39 g, 42.7 mmol) and the resulting suspension stirred for 20 minutes. A solution of iodine (4.38 g, 17.2 mmol) in dimethylformamide (5 mL) was then added, and the reaction mixture stirred for a further 45 minutes. The resulting solution was then poured into ice water (400 mL) and the precipitate collected by filtration. The resulting solid was washed with further portions of cold water and dried on the filter paper. The red powder was re-dissolved in tetrahydrofuran (5 mL) and added at 0 °C to a stirred solution of sodium hydroxide (8.7 g, 220 mmol), tetrabutylammonium bromide (0.30 g, 0.93 mmol) and tetrabutylammonium chloride (1.00 g, 3.60 mmol) in water (35 mL). To this rapidly stirring suspension was added dropwise a solution of benzenesulfonyl chloride (3.90 g, 22.1 mmol) in tetrahydrofuran (15 mL). The resulting reaction mixture was warmed to room temperature and stirred for a further three hours. The crude reaction solution was diluted with water and extracted with three portions of ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residue was passed through a plug of silica, eluting with 10% ethyl acetate in petroleum ether 40–60, to furnish *3-iodo-1-(phenylsulfonyl)-1H-indole* (3.10 g, 8.1 mmol, 47%) for direct consumption in the second step of the reaction.

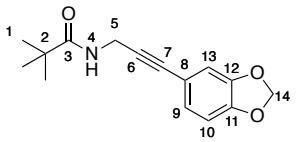
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00–7.96 (m, 1H, H-13), 7.93–7.89 (m, 2H, H-17), 7.72 (s, 1H, H-15), 7.57 (t, $\mathcal{J}$ = 7.5 Hz, 1H, H-19), 7.47 (app. t, $\mathcal{J}$ = 7.7 Hz, 2H, H-18), 7.41–7.36 (m, 2H, H-10,12), 7.35–7.30 (m, 1H, H-11). Experimental data in agreement with previous literature report.[219]

Subsequently prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (512 mg, 3.70 mmol), the freshly prepared *3-iodo-1-(phenylsulfonyl)-1H-indole* (1.55 g, 4.05 mmol), $Pd(PPh_3)_2Cl_2$ (33.4 mg, 48 mg) and CuI (18.9 mg, 0.10 mmol) in tetrahydrafuran (6 mL) with stirring for 18 hours. Crude residue purified by silica column chromatography, eluting with 20 to 50% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a yellow crystalline solid (1.25 g, 3.20 mmol, 86%).

T_m 144–147 °C; IR ν_{max}/cm^{-1} (film): 3345 (br., N–H), 2964, 1647 (C=O), 1516, 1447, 1372, 1276, 1229, 1177, 1128, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (app. dt, 1H, $\mathcal{J}$ = 8.3, 0.9 Hz, H-13), 7.91–7.87 (m, 2H, H-17), 7.73 (s, 1H, H-15), 7.61 (ddd, $\mathcal{J}$ = 7.8, 1.2, 0.8 Hz, 1H, H-10), 7.55 (tt, $\mathcal{J}$ = 7.5, 1.3 Hz, 1H, H-19), 7.47–7.42 (m, 2H, H-18), 7.36 (ddd, $\mathcal{J}$ = 8.6, 7.4, 1.2 Hz, 1H, H-12), 7.29 (ddd, $\mathcal{J}$ = 7.8, 7.4, 1.1 Hz, 1H, H-11), 5.89 (br. s, 1H, H-4), 4.33 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.24 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.0 (C-3), 137.8 (C-16), 134.15 (C-19) 135.13 (C-14), 130.7 (C-9), 129.4 (C-18),

129.1 (C-15), 126.9 (C-17), 125.6 (C-12), 123.9 (C-11), 120.5 (C-10), 113.6 (C-13), 104.8 (C-8), 89.5 (C-7), 74.4 (C-6) 38.7 (C-2), 30.4 (C-5), 27.5 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 395.1417, $C_{22}H_{23}N_2O_3S$ requires 395.1424.

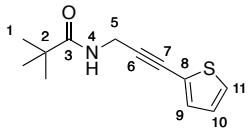
N-(3-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl)pivalamide **365a**



Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (2.02 g, 14.4 mmol), and 5-iodobenzo[*d*][1,3]dioxole (3.97 g, 16.0 mmol), $Pd(PPh_3)_2Cl_2$ (132 mg, 0.19 mmol) and CuI (74.4 mg, 0.39 mmol) in tetrahydrofuran (12 mL) with stirring for 6 hours. Crude residue purified by silica column chromatography, eluting with 20 to 40% ethyl acetate in petroleum ether 40–60 to furnish the title compound as an orange crystalline solid (2.84 g, 11.0 mmol, 76%).

T_m 83–85 °C; IR ν_{max}/cm^{-1} (film): 3337 (br., N–H), 2964, 2905, 1641 (C=O), 1502, 1489, 1441, 1330, 1245, 1209, 1102, 1037; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.93 (dd, $\mathcal{J}$ = 8.0, 1.6 Hz, 1H, H-9), 6.85 (d, $\mathcal{J}$ = 1.6 Hz, 1H, H-13), 6.72 (d, $\mathcal{J}$ = 8.0 Hz, 1H, H-10), 5.95 (s, 2H, H-14), 5.92 (br. s, 1H, H-4), 4.22 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.21 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (C-3), 148.1 (C-11), 147.5 (C-12), 126.5 (C-9), 115.9 (C-8), 111.8 (C-13), 108.5 (C-10), 101.4 (C-14), 83.5 (C-7), 83.3 (C-6), 38.8 (C-2), 30.3 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 260.1280, $C_{15}H_{18}NO_3$ requires 260.1281.

N-(3-(thiophen-2-yl)prop-2-yn-1-yl)pivalamide **366a**

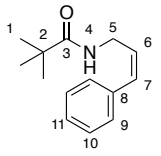


Prepared according to general procedure **A** with *N-(prop-2-yn-1-yl)pivalamide* **353** (1.97 g, 14.2 mmol), 2-iodothiophene (1.73 mL, 15.7 mmol), $Pd(PPh_3)_2Cl_2$ (129 mg, 0.18 mmol) and CuI (72.9 mg, 0.38 mmol) in tetrahydrafuran (24 mL) with stirring for 1 hour. Crude residue purified by silica column chromatography, eluting with 20 to 30% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a yellow crystalline solid (2.28 g, 10.3 mmol, 74%).

T_m 63–66 °C; IR ν_{max}/cm^{-1} (film): 3333 (br., N–H), 2964, 1645 (C=O), 1520, 1478, 1358, 1292, 1207, 1193; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.24 (dd, 1H, $\mathcal{J}$ = 5.3, 1.0 Hz, 1H, H-11), 7.20 (dd, $\mathcal{J}$ = 3.6, 1.0 Hz, 1H, H-9), 6.96 (dd, $\mathcal{J}$ = 5.3, 3.6 Hz, 1H, H-10), 5.86 (br. s, 1H, H-4), 4.28 (d, $\mathcal{J}$ = 5.0 Hz, 2H, H-5), 1.22 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.2 (C-3), 132.5 (C-9), 127.4 (C-11), 127.1 (C-10), 122.6 (C-8), 89.1 (C-7), 76.9 (C-6), 38.8 (C-2), 30.5 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 222.0948, $C_{12}H_{16}NOS$ requires 222.0947.

6.2.2.2 Alkene synthesis

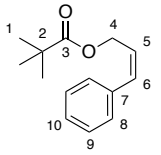
(Z)-N-(3-phenylallyl)pivalamide **315**[157]



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (955 mg, 3.84 mmol), $NaBH_4$ (145 mg, 3.84 mmol), ethylenediamine (0.90 mL, 13.4 mmol) and *N-(3-phenylprop-2-yn-1-yl)pivalamide* **315a** (4.13 g, 19.2 mmol) in a total volume of 40 mL ethanol with stirring for 5 hours. Crude product purified by silica column chromatography, eluting with a gradient of 5–20% ethyl acetate in pet. ether 40–60, to yield the title compound as a white crystalline solid (3.71 g, 17.1 mmol, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.39–7.35 (m, 2H, H-9), 7.28–7.24 (m, 3H, H-10,11), 6.59 (dt, $\mathcal{J}$ = 11.6, 1.9 Hz, 1H, H-7), 5.72–5.61 (m, 2H, H-4,6), 4.19 (ddd, $\mathcal{J}$ = 6.7, 5.5, 1.9 Hz, 2H, H-5), 1.19 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.5 (C-3), 136.6 (C-8), 131.9 (C-7), 129.0 (C-6), 128.6 (C-10), 128.6 (C-9), 127.6 (C-11), 38.9 (C-2), 38.2 (C-5), 27.8 (C-1). Experimental data in agreement with previous literature report.[157]

(Z)-3-phenylallyl pivalate **349**



Precursor prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (498 mg, 2.00 mmol), $NaBH_4$ (75.8 mg, 2.00 mmol), ethylenediamine (0.47 mL, 7.00 mmol) and 3-phenyl-2-propyn-1-ol (1.25 ml, 10.0 mmol) in a total volume of 37 mL ethanol with stirring for 18 hours. The crude reaction mixture was concentrated *in vacuo* and the residue suspended in diethyl ether (50 ml) and filtered through a plug of silica. The fitrate was concentrated *in vacuo* to give the crude intermediate *(2Z)-3-phenylprop-2-en-1-ol* (*ca.* 1.3 g, 10 mmol) as a pale yellow oil. Consumed without further purification.

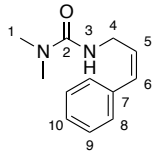
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (app. t, $\mathcal{J}$ = 7.7 Hz, 2H, H-9), 7.29 (t, $\mathcal{J}$ = 7.3 Hz, 1H, H-10), 7.24 (d, $\mathcal{J}$ = 7.5 Hz, 2H, H-8), 6.60 (d, $\mathcal{J}$ = 12.0 Hz, 1H, H-6), 5.90 (dt, $\mathcal{J}$ = 12.0, 6.4 Hz, 1H, H-5), 4.47 (dd, $\mathcal{J}$ = 6.4, 1.4 Hz, 2H, H-4), 1.51 (br. s, 1H, OH).

Pivaloyl chloride (1.35 ml, 11.0 mmol) was added dropwise at room temperature to a stirred solution of the crude *(2Z)-3-phenylprop-2-en-1-ol*, Et_3N (14.0 ml, 100 mmol) and DMAP (61 mg, 0.50 mmol) in dichloromethane (20 mL) and stirred for 3 hours. The resulting reaction mixture was then filtered through celite™ and concentrated *in vacuo* to give the crude product as a yellow oil. This residue was

purified by silica column chromatography, eluting with 0–5% diethyl in petroleum ether 40–60, to furnish the title compound as a colourless oil (1.57 g, 7.19 mmol, 72% over two steps).

R_F 0.35 (5% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2972, 1726 (C=O), 1481, 1397, 1368, 1278, 1141, 1031, 975, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.36 (m, 2H, H-8), 7.21–7.28 (m, 3H, H-9,10), 6.64 (dt, J = 12.0, 1.6 Hz, 1H, H-6), 5.79 (dt, J = 12.0, 6.4 Hz, 1H, H-5), 4.82 (dd, J = 6.4, 1.6 Hz, 2H, H-4), 1.20 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5 (C-3), 136.3 (C-7), 132.9 (C-6), 128.7 (C-9), 128.5 (C-8), 127.6 (C-10), 126.3 (C-5), 61.5 (C-4), 38.9 (C-2), 27.3 (C-1); HRMS-ESI (m/z) found $[M+NH_4]^+$ 236.1647, $C_{14}H_{22}O_2N$ requires 236.1645.

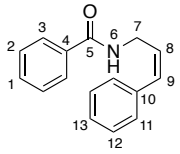
(Z)-1,1-dimethyl-3-(3-phenylallyl)urea **350**



Prepared according to general procedure **B** with $Ni(OAc)_2$•$4H_2O$ (668 mg, 2.69 mmol), $NaBH_4$ (102 mg, 2.69 mmol), ethylenediamine (0.63 mL, 9.38 mmol) and *1,1-dimethyl-3-(3-phenylprop-2-yn-1-yl)urea* **350a** (2.71 g, 13.4 mmol) in a total volume of 40 mL ethanol with stirring for 3.5 hours. Silica plug eluted with 5% methanol in dichloromethane. Crude product purified by silica column chromatography, eluting with a gradient of 0 to 3% methanol in dichloromethane to furnish the title compound as an off-white crystalline solid (2.29 g, 11.2 mmol, 84%).

T_m 80–83 °C; IR ν_{max}/cm^{-1} (film): 3339 (br., N–H), 2928, 1630 (C=O), 1528, 1494, 1374, 1221; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–7.34 (m, 2H, H-8), 7.21–7.25 (m, 3H, H-9,10), 6.52 (dt, J = 11.7, 1.8 Hz, 1H, H-6), 5.71 (dt, J = 11.7, 6.7 Hz, 1H, H-5), 4.46 (br. s, 1H, H-3), 4.13 (ddd, J = 6.7, 5.5, 1.8 Hz, 2H, H-4), 2.86 (s, 6H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4 (C-2), 136.7 (C-7), 130.8 (C-6), 130.0 (C-5), 128.9 (C-9), 128.4 (C-8), 127.2 (C-10), 39.4 (C-4), 36.3 (C-1); HRMS-ESI (m/z) found $[M+Na]^+$ 227.1155, $C_{12}H_{16}N_2NaO$ requires 227.1155.

(Z)-N-(3-phenylallyl)benzamide **351**[157]



Trifluoroacetic acid (1.99 mL, 25.8 mmol) was added dropwise to a solution of *tert-butyl (Z)-(3-phenylallyl)carbamate* **351a** (400 mg, 1.72 mmol) in dichloromethane (20 mL) and the resulting yellow solution stirred for 20 hours. The reaction mixture was then quenched with the addition of 10 % aqueous sodium hydroxide solution (10 mL), the organic layer extracted with dichloromethane (2 x 20 mL), the combined organic layers washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated *in*

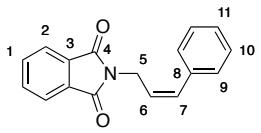
vacuo to give the free allylic amine, *(Z)-3-phenylprop-2-en-1-amine* (115 mg, 0.86 mmol) as white crystalline solid. Consumed without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (app. t, $\mathcal{J}$ = 7.6 Hz, 2H, H-12), 7.30–7.27 (m, 3H, H-11,13), 6.48 (d, $\mathcal{J}$ = 11.7 Hz, 1H, C-9), 5.76 (dt, $\mathcal{J}$ = 11.7, 6.4 Hz, 1H, H-8), 3.61 (br. s, 2H, H-7), 1.44 (br. s, 2H, H-6).

Benzoyl chloride (49 µL, 0.42 mmol) was added dropwise at 0 °C to a stirred solution of *(Z)-3-phenylprop-2-en-1-amine* (50 mg, 0.38 mmol) in dichloromethane (1 mL). The resulting reaction mixture then underwent a dropwise addition of triethylamine (31 µL, 0.42 mmol) before being warmed to room temperature and stirred for 14 hours. The resulting solution was then quenched with sat. aq. NH_4Cl solution (1 mL), extracted with dichloromethane (2 x 2 mL), and the organic fractions combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica column chromatography, eluting with 20% ethyl acetate in petroleum ether 40–60 to furnish the title product as a white crystalline solid (41 mg, 0.17 mmol, 23% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.74 (m, 2H, H-3), 7.52–7.49 (m, 1H, H-1), 7.45–7.41 (m, 2H, H-2), 7.39–7.36 (m, 2H, H-12), 7.30–7.28 (m, 3H, H-11,13), 6.66 (d, $\mathcal{J}$ = 11.6 Hz, 1H, H-9), 6.23 (br. s, 1H, H-6), 5.79 (dt, $\mathcal{J}$ = 11.6, 6.7 Hz, 1H, H-8), 4.37–4.40 (m, 2H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7 (C-5), 136.6 (C-10), 134.8 (C-4), 132.4 (C-9), 131.8 (C-1), 129.1 (C-11), 128.9 (C-2), 128.7 (C-13), 128.1 (C-8), 127.7 (C-13), 127.2 (C-3), 38.7 (C-7). Experimental data in agreement with previous literature report.[157]

(Z)-2-(3-phenylallyl)isoindoline-1,3-dione **352**



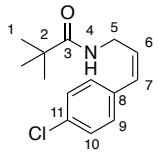
Dry triethylamine (2.79 mL, 20.0 mmol) was added dropwise to a suspension of *N*-propargylphthalimide (1.85 g, 10.0 mmol), iodobenzene (1.23 mL, 11.0 mmol), $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol) and CuI (51 mg, 0.27 mmol) in dry acetonitrile (20 mL) held at 0 °C, with the resulting brown suspension then allowed to warm to room temperature and stirred for 18 hours. The yellow reaction mixture was then concentrated *in vacuo* and the residue dissolved in ethyl acetate (50 mL). This solution was then washed with water (20 mL) and brine (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude coupled alkyne, *2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione* (2.01 g, 7.70 mmol) as an orange powder, reacted on without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (dd, $\mathcal{J}$ = 5.4, 3.2 Hz, 2H, H-1), 7.77 (dd, $\mathcal{J}$ = 5.4, 3.2 Hz, 2H, H-2), 7.46–7.42 (m, 2H, H-9), 7.32–7.27 (m, 3H, H-10,11), 4.71 (s, 2H, H-5).

Subsquently prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (383 mg, 1.54 mmol), $NaBH_4$ (56.9 mg, 1.50 mmol), ethylenediamine (0.36 mL, 5.39 mmol) and the crude alkyne, *2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione*, (2.01 g, 7.70 mmol) in a total volume of 47 mL ethanol with stirring for 6 hours. Crude product purified by silica column chromatography, eluting with a gradient of 0 to 20% ethyl acetate in a 10% solution of dichloromethane in petroleum ether 40–60, to give the solid product *(Z)-2-(3-phenylallyl)isoindoline-1,3-dione* (137 mg, 0.52 mmol, 5% over two steps) as an inseparable 10:1 mixture of alkene product to corresponding over-reduced alkane by-product.

R_F 0.24 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3044, 3026, 1771, 1702 (C=O), 1427, 1395, 1323, 1109; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84–7.80 (m, 2H, H-1), 7.71–7.67 (m, 2H, H-2), 7.38–7.36 (m, 4 H, H-9,10), 7.30 (m, 1H, H-11), 6.60 (dt, $\mathcal{J}$ = 11.6, 1.9 Hz, 1H, H-7), 5.65 (dt, $\mathcal{J}$ = 11.6, 6.4 Hz, 1H, H-6), 4.57 (dd, $\mathcal{J}$ = 6.4, 1.9 Hz, 2H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1 (C-4), 136.3 (C-8), 134.0 (C-2), 132.2 (C-3), 132.1 (C-7), 128.9 (C-9), 128.5 (C-10), 127.4 (C-11), 125.9 (C-6), 123.3 (C-1), 36.6 (C-5); HRMS-ESI (m/z) found $[M+H]^+$ 264.1018, $C_{17}H_{14}NO$ requires 264.1019.

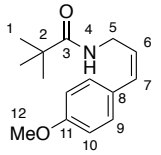
(Z)-N-(3-(4-chlorophenyl)allyl)pivalamide **356**



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (296 mg, 1.19 mmol), $NaBH_4$ (45.0 mg, 1.19 mmol), ethylenediamine (0.28 mL, 4.15 mmol) and *N-(3-(4-chlorophenyl)prop-2-yn-1-yl)pivalamide* **356a** (1.50 g, 6.00 mmol) in a total volume of 20 mL ethanol with stirring for 14 hours. Crude product purified by silica column chromatography, eluting with a gradient of 10 to 20% ethyl acetate in petroleum ether 40–60, to yield the title compound as a pale yellow crystalline solid (1.09 g, 4.3 mmol, 78%).

T_m 74–76 °C; IR ν_{max}/cm^{-1} (film): 3340 (br., N–H), 2964, 2905, 1635 (C=O), 1524, 1491, 1366, 1207, 1092, 1013; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.28 (d, $\mathcal{J}$ = 8.4 Hz, 2H, H-9), 7.14 (d, $\mathcal{J}$ = 8.4 Hz, 2H, H-10), 6.47 (d, $\mathcal{J}$ = 11.6 Hz, 1H, H-7), 5.83 (br. s, 1H, H-4), 5.63 (dt, $\mathcal{J}$ = 11.6, 6.3 Hz, 1H, H-6), 4.09 (ddd, $\mathcal{J}$ = 6.3, 5.2, 1.7 Hz, 2H, H-5), 1.16 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 178.4 (C-3), 134.9 (C-8), 133.1 (C-11), 130.2 (C-7), 130.1 (C-10), 129.3 (C-6), 128.5 (C-9), 38.7 (C-2), 38.0 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 252.1152, $C_{14}H_{19}NOCl$ requires 252.1150.

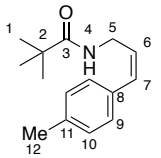
(Z)-N-(3-(4-methoxyphenyl)allyl)pivalamide **360**[157]



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (296 mg, 1.19 mmol), $NaBH_4$ (45.0 mg, 1.19 mmol), ethylenediamine (0.28 mL, 4.15 mmol) and *N-(3-(4-methoxyphenyl)prop-2-yn-1-yl)pivalamide* **360a** (1.47 g, 6.00 mmol) in a total volume of 20 mL ethanol with stirring for 24 hours. Crude product purified by silica column chromatography, eluting with a gradient of 20 to 50% ethyl acetate in petroleum ether 40–60, to yield the title compound as a white crystalline solid (1.17 g, 4.68 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-9), 6.89 (d, $\mathcal{J}$ = 8.7, Hz, 2H, H-10), 6.53 (d, $\mathcal{J}$ = 11.6 Hz, 1H, H-7), 5.67 (br. s, 1H, H-4), 5.56 (dt, $\mathcal{J}$ = 11.6, 6.7 Hz, 1H, H-6), 4.15–4.18 (m, 2H, H-5), 3.82 (s, 3H, H-12), 1.19 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.7 (C-3), 159.2 (C-11), 131.6 (C-7), 130.5 (C-9), 129.4 (C-8), 126.9 (C-6), 114.2 (C-10), 55.7 (C-12), 39.0 (C-2), 38.4 (C-5), 28.0 (C-1). Spectroscopic data consistent with those reported in the literature.[157]

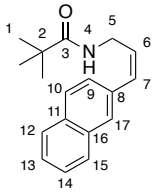
(Z)-N-(3-(p-tolyll)allyl)pivalamide **361**[157]



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (74.5 mg, 0.30 mmol), $NaBH_4$ (11.3 mg, 0.30 mmol), ethylenediamine (70 µL, 1.04 mmol) and *N-(3-(p-tolyl)prop-2-yn-1-yl)pivalamide* **361a** (344 mg, 1.50 mmol) in a total volume of 5 mL ethanol with stirring for 18 hours. Crude product purified by silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, to yield the title compound as a pale yellow crystalline solid (198 mg, 0.86 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17–7.10 (m, 4H, H-9,10), 6.54 (d, $\mathcal{J}$ = 11.6 Hz, 1H, H-7), 5.72 (br. s, 1H, H-4), 5.60 (dt, $\mathcal{J}$ = 11.6, 6.7 Hz, 1H, H-6), 4.15 (ddd, $\mathcal{J}$ = 6.7, 5.3, 1.6 Hz, 2H, H-5), 2.34 (s, 3H, H-12), 1.18 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3 (C-3), 137.2 (C-11), 133.6 (C-8), 131.7 (C-7), 129.1 (C-10), 128.8 (C-9), 127.7 (C-6), 38.7 (C-2), 38.0 (C-5), 27.6 (C-1), 21.3 (C-12). Spectroscopic data consistent with those reported in the literature.[157]

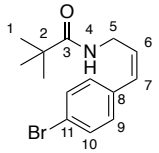
(Z)-N-(3-(naphthalen-2-yl)allyl)pivalamide **362**



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (210 mg, 0.840 mmol), $NaBH_4$ (31.9 mg, 0.840 mmol), ethylenediamine (0.200 mL, 2.95 mmol) and *N-(3-(naphthalen-2-yl)prop-2-yn-1-yl)pivalamide* **362a** (1.11 g, 4.20 mmol) in a total volume of 10 mL ethanol with stirring for 18 hours. Crude residue purified by silica column chromatography, eluting with 20% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a white crystalline solid (880 mg, 3.27 mmol, 78%).

T_m 93–97 °C; IR ν_{max}/cm^{-1} (film): 3341 (br., N–H), 3059, 2952, 1633 (C=O), 1528, 1481, 1362, 1288, 1203, 822; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84–7.79 (m, 3H, H-10,12,15), 7.68 (s, 1H, H-17), 7.51–7.45 (m, 2H, H-13,14), 7.38 (dd, $\mathcal{J}$ = 8.3, 1.7 Hz, 1H, H-9), 6.23 (dt, $\mathcal{J}$ = 11.5, 1.9 Hz, 1H, H-7), 5.74 (dt, $\mathcal{J}$ = 11.5, 5.7 Hz, 2H, H-3,6), 4.27 (ddd, $\mathcal{J}$ = 7.1, 5.7, 1.9 Hz, 2H, H-5), 1.18 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.4 (C-3), 134.0 (C-11), 133.3 (C-16), 132.6 (C-8), 131.7 (C-7), 128.9 (C-6), 128.2 (C-10), 128.0 (C-15), 127.9 (C-17), 127.7 (C-12), 127.0 (C-9), 126.4 (C-13/14), 126.2 (C-13/14), 38.8 (C-2), 38.1 (C-5), 27.7 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 268.1697, $C_{18}H_{22}NO$ requires 268.1696.

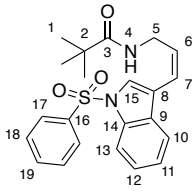
(Z)-N-(3-(4-bromophenyl)allyl)pivalamide **363**[157]



Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (287 mg, 1.15 mmol), $NaBH_4$ (43.5 mg, 1.15 mmol), ethylenediamine (0.27 mL, 4.02 mmol) and *N-(3-(4-bromophenyl)prop-2-yn-1-yl)pivalamide* **363a** (1.71 g, 5.80 mmol) in a total volume of 20 mL ethanol with stirring for 18 hours. Crude product purified by silica column chromatography, eluting with a gradient of 20 to 50% ethyl acetate in petroleum ether 40–60, to yield the title compound as a pale yellow crystalline solid (1.02 g, 3.42 mmol, 59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (d, $\mathcal{J}$ = 8.4 Hz, 2H, H-9), 7.12 (d, $\mathcal{J}$ = 8.4 Hz, 2H, H-10), 6.50 (d, $\mathcal{J}$ = 11.6 Hz, 1H, H-7), 5.73 (br. s, 1H, H-4), 5.67 (dt, $\mathcal{J}$ = 11.6, 6.6 Hz, 1H, H-6), 4.12 (td, $\mathcal{J}$ = 6.6, 1.8 Hz, 2H, H-5), 1.19 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.6 (C-3), 135.6 (C-8), 131.8 (C-10), 130.7 (C-9), 130.6 (C-7), 129.6 (C-6), 121.6 (C-11), 39.0 (C-2), 38.2 (C-5), 27.9 (C-1). Spectroscopic data consistent with those reported in the literature.[157]

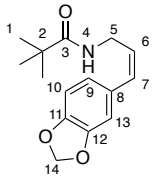
(Z)-N-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)allyl)pivalamide **364**



Prepared according to general procedure **B** with increased equivalents of $Ni(OAc)_2 \bullet 4H_2O$ (900 mg, 3.62 mmol), $NaBH_4$ (138 mg, 3.65 mmol) and ethylenediamine (0.85 mL, 12.7 mmol) and *N-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)prop-2-yn-1-yl)pivalamide* **364a** (2.40 g, 6.10 mmol) in total volume of 6 mL ethanol with stirring for 24 hours. Crude residue purified by silica column chromatography, eluting with 20 to 50% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a white crystalline solid (1.69 g, 4.27 mmol, 70%).

T_m 115–118 °C; IR ν_{max}/cm^{-1} (film): 3349 (br., N–H), 2968, 2909, 1641 (C=O), 1518, 1447, 1368, 1175, 1136, 1092, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, 1H, $\mathcal{J}$ = 8.3 Hz, H-13), 7.94–7.90 (m, 2H, H-17), 7.57–7.48 (m, 3H, H-10,15,19), 7.47–7.43 (m, 2H, H-18), 7.35 (ddd, $\mathcal{J}$ = 8.3, 7.2, 0.9 Hz, 1H, H-12), 7.27 (ddd, $\mathcal{J}$ = 7.9, 7.2, 1.1 Hz, 1H, H-11), 6.56 (app. dq, $\mathcal{J}$ = 11.3, 0.9 Hz, 1H, H-7), 5.85–5.75 (m, 2H, H-4,6), 4.33 (app. td, $\mathcal{J}$ = 6.4, 1.8 Hz, 2H, H-5), 1.22 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5 (C-3), 138.1 (C-16), 134.8 (C-14), 134.1 (C-19), 130.5 (C-9), 130.4 (C-6), 129.5 (C-18), 127.0 (C-17), 125.3 (C-12), 124.1 (C-15), 123.6 (C-11), 120.3 (C-7), 119.6 (C-10), 118.3 (C-8), 113.8 (C-13), 38.8 (C-5), 27.7 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 397.1577, $C_{22}H_{25}N_2O_3S$ requires 397.1580.

(Z)-N-(3-(benzo[d][1,3]dioxol-5-yl)allyl)pivalamide **365**

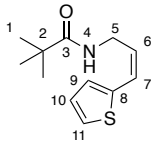


Prepared according to general procedure **B** with $Ni(OAc)_2 \bullet 4H_2O$ (487 mg, 1.96 mmol), $NaBH_4$ (74.0 mg, 1.96 mmol), ethylenediamine (0.46 mL, 6.83 mmol) and *N-(3-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl)pivalamide* **365a** (2.54 g, 9.80 mmol) in a total volume of 30 mL ethanol with stirring for 22 hours. Crude residue purified by silica column chromatography, eluting with 10 to 30% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a white crytalline solid (2.09 g, 7.94 mmol, 81%).

T_m 53–55 °C; IR ν_{max}/cm^{-1} film): 3333 (br., N–H), 2964, 2901, 1633 (C=O), 1524, 1504, 1488, 1441, 1237, 1207, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, $\mathcal{J}$ = 7.9 Hz, 1H, H-10), 6.72–6.69 (m, 2H, H-9,13), 6.45 (dt, $\mathcal{J}$ = 11.7, 1.8 Hz, 1H, H-7), 5.94 (s, 2H, H-14), 5.78 (br. s, 1H, H-4), 5.54 (dt, $\mathcal{J}$ = 11.7, 6.7 Hz, 1H, H-6), 4.12 (ddd, $\mathcal{J}$ = 6.7, 5.3, 1.8 Hz, 2H, H-5), 1.18 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4 (C-3), 147.7 (C-12), 146.8 (C-11), 131.2 (C-7), 130.5 (C-8), 127.3 (C-6), 122.7 (C-13),

109.0 (C-9), 108.3 (C-10), 101.1 (C-14), 38.7 (C-2), 38.1 (C-5), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 262.1437, $C_{15}H_{20}NO_3$ requires 262.1438.

(Z)-N-(3-(thiophen-2-yl)allyl)pivalamide **366**

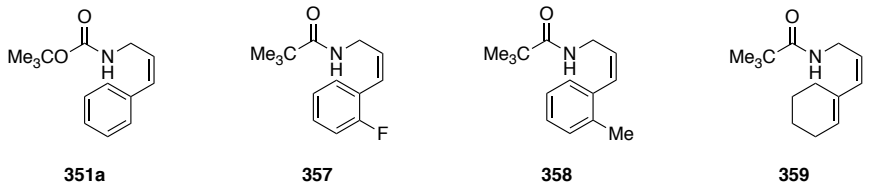


Prepared according to general procedure **B** with $Ni(OAc)_2 \cdot 4H_2O$ (502 mg, 2.03 mmol), $NaBH_4$ (76.9 mg, 2.03 mmol), ethylenediamine (0.48 mL, 7.10 mmol) and *N-(3-(thiophen-2-yl)prop-2-yn-1-yl)pivalamide* **366a** (2.24 g, 10.1 mmol) in total volume of 25 mL ethanol with stirring for 18 hours. The reaction mixture was observed to be incomplete following work-up and so was re-exposed to these conditions with increased equivalents of $NaBH_4$ (308 mg, 8.12 mmol), $Ni(OAc)_2(H_2O)_4$ (2.01 g, 8.12 mmol) and ethylene diamine (1.92 mL, 28.4 mmol) in 100 mL ethanol. Crude residue purified by silica column chromatography, eluting with 20–50% diethyl ether in petroleum ether 40–60 to furnish the title compound as an off-white solid (1.57 g, 7.00 mmol, 69%).

T_m 47–49 °C; IR ν_{max}/cm^{-1} (film): 3341 (br., N–H), 2964, 1641 (C=O), 1526, 1481, 1366, 1292, 1211, 852, 696; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.29 (br. d, $\mathcal{J}$ = 5.0 Hz, 1H, H-11), 7.02 (dd, $\mathcal{J}$ = 5.0, 3.5 Hz, 1H, H-10), 6.99 (br. d, $\mathcal{J}$ = 3.5 Hz, 1H, H-9), 6.63 (dt, $\mathcal{J}$ = 11.5, 1.7 Hz, 1H, H-7), 5.81 (br. s, 1H, H-4), 5.57 (dt, $\mathcal{J}$ = 11.5, 6.8 Hz, 1H, H-6), 4.23 (ddd, $\mathcal{J}$ = 6.8, 5.4, 1.7 Hz, 2H, H-5), 1.21 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5 (C-3), 139.3 (C-8), 128.2 (C-9), 127.3 (C-10), 126.6 (C-6), 126.2 (C-11), 124.1 (C-7), 38.8 (C-2), 38.4 (C-5), 27.7 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 224.1104, $C_{12}H_{18}NOS$ requires 224.1104.

6.2.2.3 Available alkene substrates

I am grateful to Elise Cahard for the use of a number of alkene substrates and precursors that she prepared over the course of her PhD studies (Figure 21).



351a **357** **358** **359**

Figure 21 – Substrates and precursors synthesised by Elise Cahard during her PhD studies

6.2.3. Hexafluorophosphate iodonium salt synthesis

6.2.3.1 Available iodonium salt precursors

The Gaunt laboratory maintains a stock of aryl(mesityl)iodonium triflates as reagents. Several of these iodonium salts were used during these studies (Figure 22). Full experimental procedures for the synthesis of the below aryl(mesityl)iodonium triflates have been reported by our laboratory and are not given within this document.[iii] I am grateful to previous members of the Gaunt group for this resource.

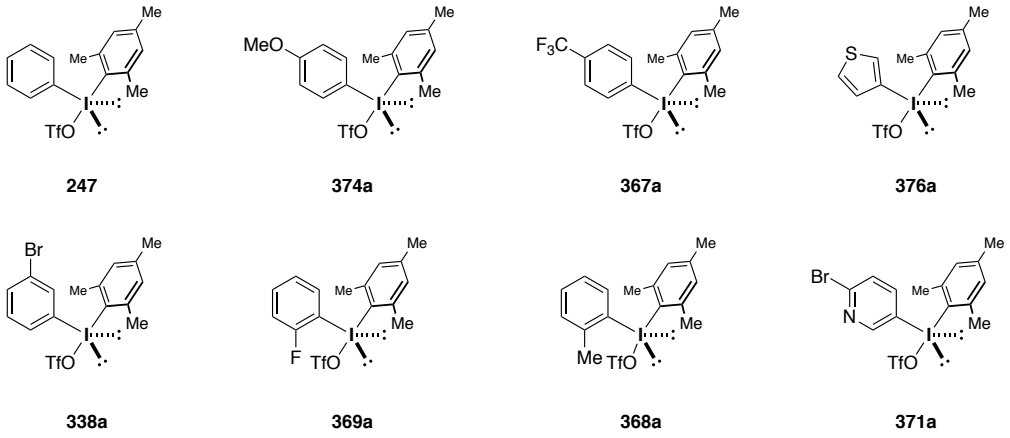
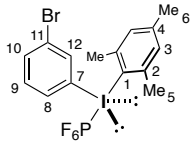


Figure 22 – Iodonium salts available within the Gaunt group

6.2.3.2 Iodonium salt synthesis

(3-bromophenyl)(mesityl)iodonium hexafluorophosphate(V) **338**[139]

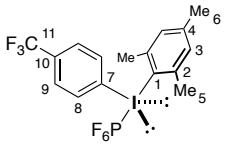


Prepared according to general procedure **C** with *(3-bromophenyl)(mesityl)iodonium triflate* **338a** (866 mg, 1.50 mmol) and sat. aq. $NaPF_6$ solution (3.0 mL) in dichloromethane (3.0 mL) with stirring for 24 hours to yield the title compound as a white powder (699 mg, 1.28 mmol, 85%).

^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.28 (app. t, $\mathcal{J}$ = 1.7 Hz, 1H, H-12), 7.89 (ddd, $\mathcal{J}$ = 7.9, 1.6, 0.8 Hz, 1H, H-8), 7.83 (ddd, $\mathcal{J}$ = 8.1, 1.8, 0.8 Hz, 1H, H-10), 7.44 (app. t, $\mathcal{J}$ = 8.1 Hz, 1H, H-9), 7.23 (s, 2H, H-3), 2.61 (s, 6H, H-5), 2.30 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 143.4 (C-4), 141.7 (C-2), 136.2 (C-11), 134.8 (C-12), 133.5 (C-8), 133.1 (C-10), 129.9 (C-3), 123.4 (C-9), 122.6 (C-1), 115.0 (C-7), 26.3 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −71.0 (d, $\mathcal{J}_{F-P}$ = 711.5 Hz). Experimental data in agreement with previous literature report.[139]

[iii] (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597; (b) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778–13781; (c) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332–5335.

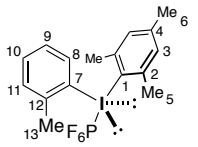
(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate(V) **367**



Prepared according to general procedure **C** with *(4-trifluoromethylphenyl)(mesityl)iodonium triflate* **367a** (1.13 g, 2.00 mmol) and sat. aq. $NaPF_6$ solution (4.0 mL) in dichloromethane (4.0 mL) with stirring for 24 hours to yield the title compound as a white powder (829 mg, 1.48 mmol, 74%).

IR ν_{max}/cm^{-1} (powder): 1596, 1399, 1322, 1179, 1132, 1064, 999, 840, 773, 739; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.14 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-8), 7.86 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-9), 7.25 (s, 2H, H-3), 2.60 (s, 6H, H-5), 2.31 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 143.5 (C-4), 141.8 (C-2), 135.1 (C-8), 131.7 (q, $^2\mathcal{J}_{C-F}$ = 32.4 Hz, C-10), 130.0 (C-3), 128.4 (q, $^3\mathcal{J}_{C-F}$ = 4.0 Hz, C-9), 123.4 (q, $^1\mathcal{J}_{C-F}$ = 274.3 Hz, C-11), 122.6 (C-1), 118.7 (q, $^5\mathcal{J}_{C-F}$ = 1.5 Hz, C-7), 26.3 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −62.6, −71.1 (d, $\mathcal{J}_{F-P}$ = 711.2 Hz); HRMS-ESI (*m/z*) found $[M–PF_6]^+$ 391.0161, $C_{16}H_{15}F_3I$ requires 391.0165.

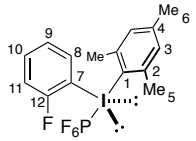
(mesityl)(o-tolyl)iodonium hexafluorophosphate(V) **368**



Prepared according to general procedure **C** with *(mesityl)(o-tolyl)iodonium triflate* **368a** (1.02 g, 2.00 mmol) and sat. aq. $NaPF_6$ solution (4.0 mL) in dichloromethane (4.0 mL) with stirring for 24 hours to yield the title compound as a white powder (792 mg, 1.64 mmol, 82%).

IR ν_{max}/cm^{-1} (powder): 3016, 1739, 1456, 1366, 1229, 822; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 7.95 (d, 1H, $\mathcal{J}$ = 8.0 Hz, H-8), 7.57–7.55 (m, 2H, H-10,11), 7.27–7.21 (m, 3H, H-9,3), 2.57–2.56 (m, 9H, H-5,13), 2.29 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 143.4 (C-4), 142.1 (C-2), 141.1 (C-12), 137.1 (C-8), 132.9 (C-10), 132.3 (C-3), 130.4 (C-11), 129.8 (C-9) 122.3 (C-1), 119.0 (C-7), 26.6 (C-5), 24.9 (C-13), 20.9 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −70.1 (d, $\mathcal{J}_{F-P}$ = 714.4 Hz); HRMS-ESI (*m/z*) found $[M–PF_6]^+$ 337.0450, $C_{16}H_{18}I$ requires 337.0448.

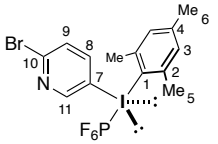
(2-fluorophenyl)(mesityl)iodonium hexafluorophosphate(V) **369**



Prepared according to general procedure **C** with *(2-fluorophenyl)(mesityl)iodonium triflate* **369a** (1.03 g, 2.00 mmol) and sat. aq. $NaPF_6$ solution (4.0 mL) in dichloromethane (4.0 mL) with stirring for 24 hours to yield the title compound as a white powder (923 mg, 1.90 mmol, 95%).

IR ν_{max}/cm^{-1} (film): 3011, 1739, 1474, 1366, 1231, 829, 759; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.26 (ddd, $\mathcal{J}$ = 8.0, 6.2, 1.3 Hz, 1H, H-10), 7.75–7.68 (m, 1H, H-8), 7.56 (app. td, $\mathcal{J}$ = 8.9, 1.3 Hz, 1H, H-9), 7.35 (dd, $\mathcal{J}$ = 8.0, 1.3 Hz, 1H, H-11), 7.20 (s, 2H, H-3), 2.62 (s, 6H, H-5), 2.28 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 159.5 (d, $^1\mathcal{J}_{C-F}$ = 248.8 Hz, C-12), 143.2 (C-4), 141.6 (C-2), 137.5 (C-8), 135.4 (d, $^3\mathcal{J}_{C-F}$ = 8.3 Hz, C-10), 129.8 (C-3), 127.6 (d, $^4\mathcal{J}_{C-F}$ = 3.0 Hz, C-9), 122.8 (C-1), 117.1 (d, $^2\mathcal{J}_{C-F}$ = 22.1 Hz, C-11), 101.5 (d, $^2\mathcal{J}_{C-F}$ = 23.5 Hz, C-7), 26.1 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: –97.6, –70.1 (d, $\mathcal{J}_{F-P}$ = 714.4 Hz); HRMS-ESI (*m/z*) found $[M\text{-}PF_6]^+$ 341.0197, $C_{15}H_{15}FI$ requires 341.0197.

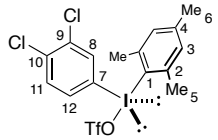
(mesityl)(6-bromopyridin-3-yl)iodonium hexafluorophosphate(V) **371**



Prepared according to general procedure **C** with *(mesityl)(6-bromopyridin-3-yl)iodonium triflate* **371a** (867 mg, 1.50 mmol) and sat. aq. $NaPF_6$ solution (3.0 mL) in dichloromethane (3.0 mL) with stirring for 24 hours to yield the title compound as an off-white powder (647 mg, 1.13 mmol, 75%).

IR ν_{max}/cm^{-1} (powder): 1541, 1435, 1355, 1281, 1240, 1086, 979, 843, 826, 809; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.89 (d, $\mathcal{J}$ = 2.4 Hz, 1H, H-11), 8.29 (dd, $\mathcal{J}$ = 8.6, 2.4 Hz, 1H, H-8), 7.80 (d, $\mathcal{J}$ = 8.6 Hz, 1H, H-9), 7.23 (s, 2H, H-3), 2.61 (s, 6H, H-5), 2.30 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 153.9 (C-11), 144.6 (C-8), 144.4 (C-10), 143.5 (C-4), 141.7 (C-2), 131.4 (C-9), 129.9 (C-3), 122.8 (C-1), 113.0 (C-7), 26.3 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: –70.1 (d, $\mathcal{J}_{F-P}$ = 711.7 Hz); HRMS-ESI (*m/z*) found $[M–PF_6]^+$ 401.9346, $C_{14}H_{14}NBrI$ requires 401.9349.

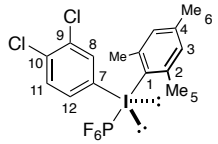
(3,4-dichlorophenyl)(mesityl)iodonium trifluoromethanesulfonate **372a**



Adapted from a procedure reported by Olofsson et al.[3] Trifluoromethanesulfonic acid (0.66 mL, 7.5 mmol) was added dropwise to a stirred solution of 1,2-dichloro-4-iodobenzene (1.36 g, 5.0 mmol) and *m*CPBA (70%, 1.27 g, 5.5 mmol - previously dried *in vacuo* for 2 hours) in dichloromethane (10 mL) held at 0 °C. The resulting yellow suspension was warmed to room temperature and stirred for a further two hours before being cooled back to 0 °C and undergoing a dropwise addition of mesitylene (0.77 mL, 5.5 mmol). The resulting orange suspension was warmed to room temperature and stirred for 15 hours. The reaction mixture was then concentrated *in vacuo* and the residue precipitated with cold diethyl ether (10 mL). The solid was collected by filtration, washed on the filter with further portions of cold diethyl ether (3 x 5 mL) and dried *in vacuo* to yield the corresponding triflate as a white microcrystalline solid (2.46 g, 4.55 mmol, 91%).

T_m 161–164 °C; IR ν_{max}/cm^{-1} (powder): 1586, 1567, 1457, 1372, 1259, 1249, 1221, 1175, 1138, 1027; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ: 8.36 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-8), 7.85 (dd, $\mathcal{J}$ = 8.6, 2.2 Hz, 1H, H-12), 7.75 (d, $\mathcal{J}$ = 8.6 Hz, 1H, H-11), 7.24 (s, 2H, H-3), 2.60 (s, 6H, H-5), 2.31 (s, 3H, H-6); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ: 143.5 (C-4), 141.8 (C-2), 135.7 (C-8), 135.4 (C-10), 134.3 (C-12), 133.5 (C-9), 133.4 (C-11), 129.9 (C-3), 122.8 (C-1), 120.7 (q, $^1\mathcal{J}_{C-F}$ = 322.3 Hz, C-Tf), 112.4 (C-7), 26.3 (C-5), 20.6 (C-6); ^{19}F NMR (376 MHz, d$_6$-DMSO) δ: −77.7; HRMS-ESI (*m/z*) found [M–OTf]$^+$ 390.9514, $C_{15}H_{14}Cl_2I$ requires 390.9512.

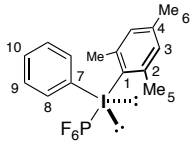
(3,4-dichlorophenyl)(mesityl)iodonium hexafluorophosphate(V) **372**



Prepared according to general procedure **C** with *(3,4-dichlorophenyl)(mesityl)iodonium triflate* **372a** (1.13 g, 2.00 mmol) and sat. aq. $NaPF_6$ solution (4.0 mL) in dichloromethane (4.0 mL) with stirring for 24 hours to yield the title compound as a white powder (978 mg, 1.82 mmol, 91%).

IR ν_{max}/cm^{-1} (powder): 1588, 1560, 1453, 1380, 1368, 1302, 1251, 1136, 1027, 824; ^{1}H NMR (500 MHz, d$_6$-DMSO) δ: 8.35 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-8), 7.84 (dd, $\mathcal{J}$ = 8.7, 2.2 Hz, 1H, H-12), 7.75 (d, $\mathcal{J}$ = 8.7 Hz, 1H, H-11), 7.24 (s, 2H, H-3), 2.60 (s, 6H, H-5), 2.31 (s, 3H, H-6); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ: 143.5 (C-4), 141.9 (C-2), 135.7 (C-8), 135.4 (C-10), 134.3 (C-12), 133.6 (C-9), 133.5 (C-11), 130.0 (C-3), 122.9 (C-1), 112.5 (C-7), 26.4 (C-5), 20.6 (C-6); ^{19}F NMR (376 MHz, d$_6$-DMSO) δ: −71.1 (d, $\mathcal{J}_{F-P}$ = 711.3 Hz); HRMS-ESI (*m/z*) found [M–PF_6]$^+$ 390.9500, $C_{15}H_{14}Cl_2I$ requires 390.9512.

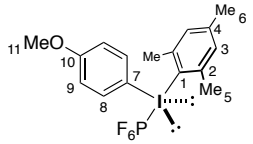
(mesityl)(phenyl)iodonium hexafluorophosphate(V) **373**



Prepared according to general procedure **C** with *(mesityl)(phenyl)iodonium triflate* **247** (748 mg, 1.50 mmol) and sat. aq. $NaPF_6$ solution (3.0 mL) in dichloromethane (3.0 mL) with stirring for 24 hours to yield the title compound as a white powder (554 mg, 1.18 mmol, 79%).

IR ν_{max}/cm^{-1} (powder): 1582, 1471, 1447, 1302, 1243, 1029, 991, 979, 824, 745; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 7.99 (d, $\mathcal{J}$ = 7.4 Hz, 2H, H-8), 7.63 (t, $\mathcal{J}$ = 7.5 Hz, 1H, H-10), 7.50 (app. t, $\mathcal{J}$ = 7.8 Hz, 2H, H-9), 7.22 (s, 2H, H-3), 2.61 (s, 6H, H-5), 2.29 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 143.2 (C-4), 141.6 (C-2), 134.5 (C-9), 131.9 (C-10), 131.8 (C-8), 129.8 (C-3), 122.6 (C-1), 114.5 (C-7), 26.3 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −71.0 (d, $\mathcal{J}_{F-P}$ = 711.4 Hz); HRMS-ESI (*m/z*) found $[M-PF_6]^+$ 323.0291, $C_{15}H_{16}I$ requires 323.0291.

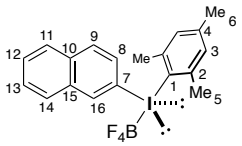
(4-methoxyphenyl)(mesityl)iodonium hexafluorophosphate(V) **374**[139]



Prepared according to general procedure **C** with *(4-methoxyphenyl)(mesityl)iodonium triflate* **374a** (793 mg, 1.50 mmol) and sat. aq. $NaPF_6$ solution (3.0 mL) in dichloromethane (3.0 mL) with stirring for 24 hours to yield the title compound as a white powder (663 mg, 1.33 mmol, 87%).

^{1}H NMR (400 MHz, d_6-DMSO) δ: 7.93 (d, $\mathcal{J}$ = 9.1 Hz, 2H, H-8), 7.19 (s, 2H, H-3), 7.04 (d, $\mathcal{J}$ = 9.1 Hz, 2H, H-9), 3.78 (s, 3H, H-11), 2.62 (s, 6H, H-5), 2.28 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 161.8 (C-10), 142.9 (C-4), 141.4 (C-2), 136.6 (C-8), 129.7 (C-3), 123.1 (C-1), 117.5 (C-9), 103.4 (C-7), 55.7 (C-11), 26.2 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −71.1 (d, $\mathcal{J}_{F-P}$ = 711.5 Hz). Experimental data in agreement with previous literature report.[6]

(2-napthyl)(mesityl)iodonium tetrafluoroborate **375a**

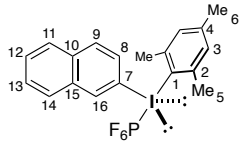


Boron trifluoride diethyl etherate (0.400 mL, 3.30 mmol) was added dropwise at 0 °C to a stirred solution of 2-napthylboronic acid (516 mg, 3.00 mmol) in dichloromethane (30 mL). To this suspension was added a solution of iodomesitylene diacetate (1.20 g, 3.30 mmol) in dichloromethane (10 mL) and the resulting solution was stirred at 0 °C for two hours. The reaction was quenched upon the addition of sat.

aq. $NaBF_4$ solution (60 mL) and the resulting biphasic mixture was stirred vigorously for a further thirty minutes. The phases were then separated and the aqueous layer extracted with dichloromethane (2 x 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The solid residues were suspended in diethyl ether (20 mL), vigorously stirred for 15 minutes and then stored at − 18 °C for 18 hours. The resulting cold suspension was filtered and the solid washed with further quantities of diethyl ether to furnish the title compound as a brown powder (1.09 g, 2.37 mmol, 79%).

IR ν_{max}/cm^{-1} (powder): 1576, 1499, 1453, 1443, 1386, 1347, 1303, 1282, 1046, 1029, 930; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ: 8.72 (s, 1H, H-16), 8.07–7.90 (m, 4H, H-8,9,11,14), 7.69–7.60 (m, 2H, H-12,13), 7.16 (s, 2H, H-3), 2.64 (s, 6H, H-5), 2.22 (s, 3H, H-6); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ: 143.5 (C-4), 141.9 (C-2), 135.8 (C-16), 134.3 (C-15), 133.6 (C-10), 131.9 (C-9), 130.1 (C-3), 130.0 (C-8), 129.2 (C-12), 128.4 (C-14), 128.34 (C-11), 128.26 (C-13), 123.0 (C-1), 111.7 (C-7), 26.7 (C-5), 20.7 (C-6); ^{19}F NMR (376 MHz, d$_6$-DMSO) δ: [−148.9, −149.0]; HRMS-ESI (*m/z*) found $[M–BF_4]^+$ 373.0438, $C_{19}H_{18}I$ requires 373.0448.

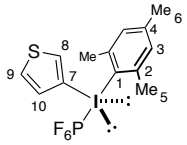
(2-napthyl)(mesityl)iodonium hexafluorophosphate(V) **375**



Prepared according to general procedure **C** with *(2-napthyl)(mesityl)iodonium tetrafluoroborate* **375a** (972 mg, 2.00 mmol) and sat. aq. $NaPF_6$ solution (4.0 mL) in dichloromethane (4.0 mL) with stirring for 20 hours to yield the title compound as a white powder (890 mg, 1.72 mmol, 86%).

IR ν_{max}/cm^{-1} (film): 3079, 2990, 2925, 1576, 1500, 1450, 1381, 1301, 1132, 931, 825; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ: 8.72 (s, 1H, H-16), 8.07–7.96 (m, 3H, H-9,11,14), 7.93 (dd, $\mathcal{J}$ = 8.8, 1.6 Hz, 1H, H-8), 7.69–7.60 (m, 2H, H-12,13), 7.17 (s, 2H, H-3), 2.64 (s, 6H, H-5), 2.24 (s, 3H, H-6); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ: 143.6 (C-4), 141.9 (C-2), 135.8 (C-16), 134.3 (C-15), 133.6 (C-10), 131.9 (C-9), 130.1 (C-3), 130.0 (C-8), 129.2 (C-12), 128.4 (C-14), 128.4 (C-11), 128.3 (C-13), 123.0 (C-1), 111.7 (C-7), 26.7 (C-5), 20.7 (C-6); ^{19}F NMR (376 MHz, d$_6$-DMSO) δ: −70.0 (d, $\mathcal{J}_{F–P}$ = 711.7 Hz); HRMS-ESI (*m/z*) found $[M–PF_6]^+$ 373.0446, $C_{16}H_{18}I$ requires 373.0448;

(thiophen-3-yl)(mesityl)iodonium hexafluorophosphate(V) **376**

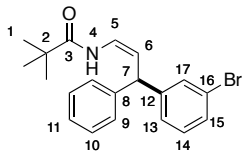


Prepared according to general procedure **C** with *(thiophen-3-yl)(mesityl)iodonium triflate* **376a** (756 mg, 1.50 mmol) and sat. aq. $NaPF_6$ solution (3.0 mL) in dichloromethane (3.0 mL) with stirring for 24 hours to yield the title compound as a white powder (636 mg, 1.16 mmol, 77%).

IR ν_{max}/cm^{-1} (powder): 1576, 1451, 1381, 1302, 1201, 1080, 1035, 981, 824, 773; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.50 (dd, $\mathcal{J}$ = 2.9, 1.2 Hz, 1H, H-8), 7.79 (dd, $\mathcal{J}$ = 5.2, 2.9 Hz, 1H, H-9), 7.53 (dd, $\mathcal{J}$ = 5.2, 1.2 Hz, 1H, H-10), 7.20 (s, 2H, H-3), 2.63 (s, 6H, H-5), 2.28 (s, 3H, H-6); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 143.0 (C-4), 141.2 (C-2), 135.2 (C-8), 131.3 (C-9), 130.7 (C-10), 129.7 (C-3), 123.6 (C-1), 98.8 (C-7), 26.3 (C-5), 20.5 (C-6); ^{19}F NMR (376 MHz, d_6-DMSO) δ: −70.2 (d, $\mathcal{J}_{F-P}$ = 711.5 Hz); HRMS-ESI (*m/z*) found $[M-PF_6]^+$ 328.9854, $C_{13}H_{14}IS$ requires 328.9855.

6.2.4. Enamide products and derivatives

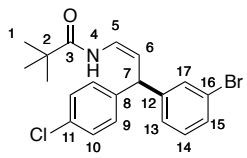
(R)-N-[(1Z)-3-(3-bromophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **332**



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (109 mg, 0.500 mmol), *(3-bromophenyl)(mesityl)iodonium hexafluorophosphate* **338** (547 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50.0 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 20% ethyl acetate in petroleum ether 40–60, provided the title compound as a white amorphous solid (102 mg, 0.280 mmol, 55%).

R_F 0.50 (20% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2963, 2849, 2321, 1649 (C=O), 1487, 1277, 1181, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (app. t, $\mathcal{J}$ = 2.5 Hz, 1H, H-17), 7.32–7.39 (m, 3H, H-10,13), 7.26–7.29 (m, 3H, H-9,11), 7.18–7.21 (m, 2H, H-14,15), 6.91 (ddd, $\mathcal{J}$ = 10.7, 8.6, 1.9 Hz, 1H, H-5), 6.84 (br. d, $\mathcal{J}$ = 10.7 Hz, 1H, H-4), 5.17 (dd, $\mathcal{J}$ = 8.6 Hz, 5.9 Hz, 1H, H-6), 4.78 (dd, $\mathcal{J}$ = 5.9, 1.9 Hz, 1H, H-7), 0.96 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6 (C-3), 146.1 (C-12), 142.7 (C-8), 131.3 (C-17), 130.6 (C-14), 130.1 (C-13), 129.3 (C-10), 128.3 (C-9), 127.4 (C-11), 126.9 (C-15), 123.2 (C-5), 123.1 (C-16), 111.9 (C-6), 49.1 (C-7), 38.8 (C-2), 27.2 (C-1); HRMS-ESI (*m/z*) found $[M]^+$ 372.0963, $C_{20}H_{22}NOBr$ requires 372.0958; $[\alpha]^{20}_D$ = −8.2 ° (c = 1.0, $CHCl_3$), calculated with sample *e.e.* of 92%; HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 219 nm) indicated 95% *e.e.*: t_R (minor) = 9.24 minutes, t_R (major) = 12.57 minutes.

(R)-N-[(1Z)-3-(3-bromophenyl)-3-(4-chlorophenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **378**

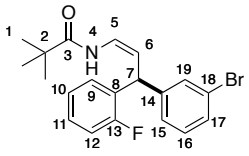


Prepared according to general procedure **D** with *(Z)-N-(3-(4-chlorophenyl)allyl)pivalamide* **356** (126 mg, 0.50 mmol), *(3-bromophenyl)(mesityl)iodonium hexafluorophosphate* **338** (547 mg, 1.00 mmol), 2,6-di-*tert*-butyl

pyridine (225 μL, 1.00 mmol) and Cu-BOX complex **248** (500 μL, 0.1 M, 50 μmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 20% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (86.0 mg, 0.21 mmol, 42%).

R_F 0.40 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3436 (br., N–H), 2968, 1683, 1653 (C=O), 1590, 1566, 1485, 1272, 1177, 1094, 1013, 785; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.37 (m, 2H, H-13,17), 7.32 (d, $\mathcal{J}$ = 8.1 Hz, 2H, H-10), 7.25–7.15 (m, 4H, H-9,14,15), 6.92 (ddd, $\mathcal{J}$ = 10.9, 8.8, 1.9 Hz, 1H, H-5), 6.84 (br. d, $\mathcal{J}$ = 10.9 Hz, 1H, H-4), 5.13 (dd, $\mathcal{J}$ = 8.8, 6.0 Hz, 1H, H-6), 4.76 (d, $\mathcal{J}$ = 6.0 Hz, 1H, H-7), 0.99 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6 (C-3), 145.5 (C-12), 141.3 (C-8), 133.2 (C-11), 131.2 (C-17), 130.8 (C-14), 130.4 (C-13), 129.6 (C-9), 129.4 (C-10), 126.9 (C-15), 123.4 (C-5), 123.3 (C-16), 111.3 (C-6), 48.2 (C-7), 38.9 (C-2), 27.2 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 408.0546, $C_{20}H_{22}NOClBr$ requires 408.0545; $[\alpha]^{20}_D$ = +2.2 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 231 nm) indicated 93% *e.e.*: t_R (major) = 10.81 minutes, t_R (minor) = 11.73 minutes.

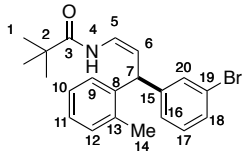
(S)-N-[(1Z)-3-(3-bromophenyl)-3-(2-fluorophenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **379**



Prepared according to general procedure **D** with *(Z)-N-(3-(2-fluorophenyl)allyl)pivalamide* **357** (118 mg, 0.50 mmol), *(3-bromophenyl)(mesityl)iodonium hexafluorophosphate* **338** (547 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 μL, 1.00 mmol) and Cu-BOX complex **248** (500 μL, 0.1 M, 50 μmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 20% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (25.0 mg, 0.06 mmol, 12%).

R_F 0.40 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3448 (br., N–H), 3349, 2964, 1677, 1649 (C=O), 1588, 1483, 1456, 1399, 1253, 1223, 1175, 1090, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (app. t, $\mathcal{J}$ = 1.7 Hz, 1H, H-19), 7.39 (app. dt, $\mathcal{J}$ = 7.4, 1.6 Hz, 1H, H-17), 7.29–7.20 (m, 4H, H-9,11,15,16), 7.14 (app. td, $\mathcal{J}$ = 7.7, 1.7 Hz, 1H, H-10), 7.11–7.03 (m, 2H, H-4,12), 6.92 (dd, $\mathcal{J}$ = 10.9, 8.2 Hz, 1H, H-5), 5.20–5.11 (m, 2H, H-6,7), 1.05 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.7 (C-3), 160.4 (d, $^1\mathcal{J}_{C-F}$ = 246.1 Hz, C-13), 144.6 (C-14), 131.2 (C-19), 130.6 (C-16), 130.3 (C-17), 129.8 (d, $^2\mathcal{J}_{C-F}$ = 15.1 Hz, C-8), 129.6 (d, $^3\mathcal{J}_{C-F}$ = 3.9 Hz, C-9), 129.0 (d, $^3\mathcal{J}_{C-F}$ = 8.4 Hz, C-11), 126.9 (C-15), 125.0 (d, $^4\mathcal{J}_{C-F}$ = 3.5 Hz, C-10), 123.3 (C-5), 123.1 (C-18), 115.9 (d, $^2\mathcal{J}_{C-F}$ = 22.5 Hz, C-12), 110.6 (C-6), 40.7 (d, $^3\mathcal{J}_{C-F}$ = 2.8 Hz, C-7), 38.9 (C-2), 27.2 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$390.0858, $C_{20}H_{22}NOFBr$ requires 390.0863; $[\alpha]^{22}_D$ = –23.4 ° (c = 1.3, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 200 nm) indicated 89% *e.e.*: t_R (minor) = 8.36 minutes, t_R (major) = 11.87 minutes.

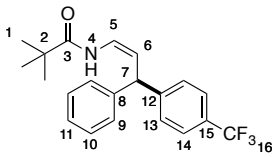
(S)-N-[(1Z)-3-(3-bromophenyl)-3-(2-methylphenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **380**



Prepared according to general procedure **D** with *(Z)-N-(3-(o-tolyl)allyl)pivalamide* **358** (116 mg, 0.50 mmol), *(3-bromophenyl)(mesityl)iodonium hexafluorophosphate* **338** (547 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 20% ethyl acetate in petroleum ether 40–60, provided the title compound as an amorphous white solid (67 mg, 0.17 mmol, 34%).

R_F 0.38 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3429 (br., N–H), 2964, 1679, 1647 (C=O), 1593, 1566, 1479, 1461, 1179, 1072, 935, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41–7.36 (m, 2H, H-18,20), 7.24–7.13 (m, 6H, H-9,10,11,12,16,17), 6.90 (ddd, $\mathcal{J}$ = 10.5, 8.8, 1.5 Hz, 1H, H-5), 6.82 (br. d, $\mathcal{J}$ = 10.5 Hz, 1H, H-4), 5.10 (dd, $\mathcal{J}$ = 8.8, 5.9 Hz, 1H, H-6), 4.97 (dd, $\mathcal{J}$ = 5.9, 1.5 Hz, 1H, H-7), 2.32 (s, 3H, H-14), 0.93 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 145.4 (C-15), 140.4 (C-8), 136.5 (C-13), 131.6 (C-20), 131.3 (C-12), 130.5 (C-16), 130.1 (C-18), 128.6 (C-10), 127.5 (C-11), 127.3 (C-17), 127.0 (C-9), 123.2 (C-19), 123.1 (C-5), 111.6 (C-6), 45.8 (C-7), 38.8 (C-2), 27.1 (C-1), 19.9 (C-14); HRMS-ESI (*m/z*) found $[M+H]^+$ 386.1105, $C_{21}H_{25}NOBr$ requires 386.1114; $[\alpha]^{20}_D$ = –29.3 ^{o} (c = 1.0, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 204 nm) indicated 97% *e.e.*: t_R (minor) = 8.02 minutes, t_R (major) = 11.04 minutes.

(R)-2,2-dimethyl-N-[(1Z)-3-phenyl-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **383**

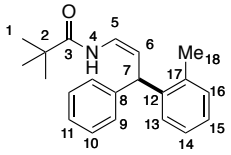


Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (108 mg, 0.50 mmol), *(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate* **367** (536 mg, 1.0 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (126 mg, 0.35 mmol, 70%).

R_F 0.44 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3670, 3424 (br., N–H), 2972, 2901, 1651 (C=O), 1484, 1326, 1249, 1165, 1118, 1066; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-14), 7.42–7.34 (m, 4H, H-10,13), 7.32–7.27 (m, 3H, H-9,11), 6.93 (ddd, $\mathcal{J}$ = 11.0, 9.2, 2.2 Hz, 1H, H-5), 6.84 (br. d, $\mathcal{J}$ = 11.0 Hz, 1H, H-4), 5.20 (dd, $\mathcal{J}$ = 9.2, 6.0 Hz, 1H, H-6), 4.89 (d, $\mathcal{J}$ = 6.0 Hz, 1H, H-7), 0.95 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 147.9 (C-12), 142.5 (C-8), 129.4 (C-10), 129.1 (q, $^2\mathcal{J}_{C–F}$ = 32.4 Hz, C-15), 128.6 (C-13), 128.4 (C-9), 127.5 (C-11), 126.0 (q, $^3\mathcal{J}_{C–F}$ = 3.1

Hz, C-14), 124.2 (q, $^{1}\mathcal{J}_{C-F}$ = 272.5 Hz, C-16), 123.2 (C-5), 111.6 (C-6), 49.2 (C-7), 38.8 (C-2), 27.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 362.1726, $C_{21}H_{23}F_3NO$ requires 362.1726; $[\alpha]^{22}_D$ = −10.0 ° (c = 1.1, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 217 nm) indicated 91% *e.e.*: t_R (minor) = 7.20 minutes, t_R (major) = 9.14 minutes.

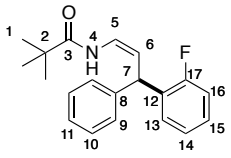
(R)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-phenylprop-1-en-1-yl]propanamide **384**



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (108 mg, 0.50 mmol), *(2-methylphenyl)(mesityl)iodonium hexafluorophosphate* **368** (482 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as an amorphous white solid (61 mg, 0.20 mmol, 40%).

R_F 0.48 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3671, 3437 (br., N–H), 2968, 2909, 1691 (C=O), 1651, 1485, 1459, 1171, 1072, 1056; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.20 (m, 2H, H-10), 7.27–7.16 (m, 7H, H-9,11,13,14,15,16), 6.89 (ddd, $\mathcal{J}$ = 10.5, 9.1, 1.8 Hz, 1H, H-5), 6.82 (br. d, $\mathcal{J}$ = 10.5 Hz, 1H, H-4), 5.14 (dd, $\mathcal{J}$ = 9.1, 5.8 Hz, 1H, H-6), 5.01 (dd, $\mathcal{J}$ = 5.8, 1.8 Hz, 1H, H-7), 2.33 (s, 3H, H-18), 0.91 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 142.8 (C-8), 141.2 (C-12), 136.5 (C-17), 131.0 (C-16), 129.0 (C-10), 128.7 (C-9), 128.6 (C-11), 127.2 (C-15), 126.9 (C-14), 126.8 (C-13), 122.8 (C-5), 112.4 (C-6), 46.2 (C-7), 38.7 (C-2), 27.1 (C-1), 19.9 (C-18); HRMS-ESI (*m/z*) found $[M+H]^+$ 308.2011, $C_{21}H_{26}NO$ requires 308.2009; $[\alpha]^{22}_D$ = +19.9 ° (c = 0.9, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 228 nm) indicated 97% *e.e.*: t_R (major) = 7.74 minutes, t_R (minor) = 8.57 minutes.

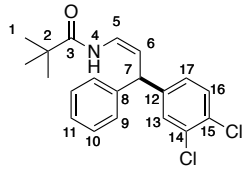
(R)-N-[(1Z)-3-(2-fluorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **385**



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (108 mg, 0.50 mmol), *(2-fluorophenyl)(mesityl)iodonium hexafluorophosphate* **369** (486 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as an amorphous white solid (65 mg, 0.21 mmol, 42%).

R_F 0.44 (20% EtOAc in pet. ether 40-60); IR ν_{max}/cm^{-1} (film): 3667 (br., N–H), 3440, 2972, 2899, 1687 (C=O), 1651, 1483, 1455, 1225, 1175, 755, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.31 (m, 4H, H-9,10), 7.30–7.21 (m, 3H, H-11,13,15), 7.13 (app. td, J = 7.8, 1.1 Hz, 1H, H-14), 7.10–7.00 (m, 2H, H-4,16), 6.92 (ddd, J = 10.9, 8.2, 0.5 Hz, 1H, H-5), 5.25–5.17 (m, 2H, H-6,7), 1.02 (s, 1H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 160.4 (d, $^1J_{C-F}$ = 243.9 Hz, C-17), 142.2 (C-8), 130.7 (d, $^2J_{C-F}$ = 17.7 Hz, C-12), 129.7 (d, $^3J_{C-F}$ = 3.1 Hz, C-13), 129.1 (C-10), 128.6 (d, $^3J_{C-F}$ = 8.7 Hz, C-15), 128.3 (C-9), 127.1 (C-11), 124.8 (d, $^4J_{C-F}$ = 2.5 Hz, C-14), 123.0 (C-5), 115.7 (d, $^2J_{C-F}$ = 21.5 Hz, C-16), 111.4 (C-6), 41.2 (C-7), 38.8 (C-2), 27.2 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 312.1760, $C_{20}H_{23}NOF$ requires 312.1758; $[\alpha]^{22}_D$ = –54.3 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 10% *i*-PrOH in *n*-hexane, 1 mL/min, 209 nm) indicated >98% ee: t_R (major) = 13.08 minutes, t_R (minor) = 13.79 minutes.

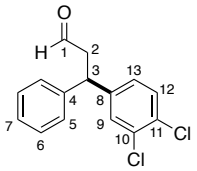
(R)-N-[(1Z)-3-(3,4-dichlorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **389**



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (108 mg, 0.50 mmol), *(3,4-dichlorophenyl)(mesityl)iodonium hexafluorophosphate* **372** (537 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as an amorphous white solid (105 mg, 0.29 mmol, 58%).

R_F 0.43 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3671 (br., N–H), 3428, 2672, 2904, 2325, 1649 (C=O), 1485, 1467, 1395, 1179, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41–7.33 (m, 4H, H-10,13,16), 7.31–7.24 (m, 3H, H-9,11), 7.11 (ddd, J = 8.3, 2.1, 0.4 Hz, 1H, H-17), 6.92 (ddd, J = 11.0, 8.9 Hz, 1.7 Hz, 1H, H-5), 6.84 (br. d, J = 11.0 Hz, 1H, H-4), 5.14 (dd, J = 8.9, 5.9 Hz, 1H, H-6), 4.78 (dd, J = 5.9, 1.7 Hz, 1H, H-7), 0.97 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 144.1 (C-12), 142.3 (C-8), 133.0 (C-14), 131.0 (C-15), 130.9 (C-16), 130.1 (C-13), 129.5 (C-10), 128.3 (C-9), 127.6 (2C, C-11,17), 123.5 (C-5), 111.3 (C-6), 48.5 (C-7), 38.8 (C-2), 27.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 362.1076, $C_{20}H_{22}NOCl_2$ requires 362.1073; $[\alpha]^{22}_D$ = –15.9 ° (c = 0.8, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 246 nm) indicated 93% *e.e.*: t_R (minor) = 9.34 minutes, t_R (major) = 20.85 minutes.

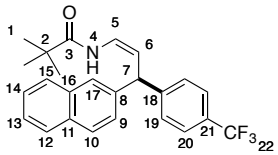
(R)-3-(3,4-dichlorophenyl)-3-phenylpropanal **436**[165]



To a stirred solution of *(R)-N-[(1Z)-3-(3,4-dichlorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide* **389** (91 mg, 0.25 mmol, 94% *e.e.*) in tetrahydrofuran (10 mL) was added concentrated hydrochloric acid (0.50 mL, 37% aqueous w/v solution) and the resulting yellow solution stirred for two hours at room temperature before undergoing a portion-wise addition of sodium carbonate (1.00 g). The suspension was stirred for a further fifteen minutes, filtered through anhydrous Na_2SO_3 and concentrated *in vacuo*. The crude residue was purified by silica column chromatography, eluting with 2 to 20% ethyl acetate in hexane, to give the title compound as a pale yellow oil (59 mg, 0.21 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (t, $\mathcal{J}$ = 1.5 Hz, 1H, H-1), 7.37 (d, $\mathcal{J}$ = 8.3 Hz, 1H, H-12) 7.35–7.29 (m, 3H, H-6,9), 7.26–7.18 (m, 3H, H-5,7), 7.08 (dd, $\mathcal{J}$ = 8.3, 2.2 Hz, 1H, H-13), 4.60 (app. t, $\mathcal{J}$ = 7.7 Hz, 1H, H-3), 3.23–3.11 (m, 2H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.0 (C-1), 143.8 (C-8), 142.2 (C-4), 132.8 (C-10), 130.9 (C-11), 130.8 (C-12), 129.8 (C-9), 129.1 (C-6), 127.7 (C-5), 127.3 (2C, C-7,13), 49.3 (C-2), 44.1 (C-3); $[\alpha]^{24}_D$ = −11.1 ° (1.05, $CHCl_3$), lit. $[\alpha]^{25}_D$ = −7.3 ° (c = 0.95, $CHCl_3$, 93% *e.e.*); HPLC analysis of the alcohol derivative ($NaBH_4$ treatment in MeOH/CH_2Cl_2) (AD-H, 2% *i*-PrOH in *n*-hexane, 1 mL/min, 209 nm) indicated 94% ee: t_R (major) = 33.54 minutes, t_R (minor) = 35.15 minutes. Experimental data in agreement with previous literature report.[165]

(S)-2,2-dimethyl-N-[(1Z)-3-(naphthalen-2-yl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **396**

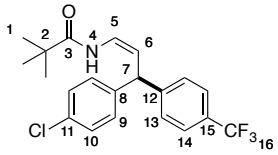


Prepared according to general procedure **D** with *(Z)-N-(3-(naphthalen-2-yl)allyl)pivalamide* **362** (134 mg, 0.50 mmol), *(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate* **367** (536 mg, 1.0 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 10% ethyl acetate in petroleum ether 40–60, provided the title compound as a yellow oil (107 mg, 0.26 mmol, 52%).

R_F 0.40 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3687 (br., N–H), 2972, 2904, 1651 (C=O), 1483, 1465, 1322, 1259, 1165, 1118, 1068, 1021, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87–7.78 (m, 3H, H-10,13,14), 7.73 (s, 1H, H-17), 7.61 (d, $\mathcal{J}$ = 8.2 Hz, 2H, H-20), 7.54–7.47 (m, 2H, H-12,15), 7.45 (d, $\mathcal{J}$ = 8.2 Hz, 2H, H-19), 7.39 (dd, $\mathcal{J}$ = 8.6, 2.1 Hz, 1H, H-9), 7.00 (ddd, $\mathcal{J}$ = 10.8, 8.8, 2.2 Hz, 1H, H-

5), 6.92 (br. d, $\mathcal{J}$ = 10.8 Hz, 1H, H-4), 5.29 (dd, $\mathcal{J}$ = 8.8, 6.2 Hz, 1H, H-6), 5.07 (d, $\mathcal{J}$ = 6.2 Hz, 1H, H-7), 0.86 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6 (C-3), 147.6 (C-18), 139.8 (C-8), 133.6 (C-15), 132.6 (C-11), 129.3 (C-10), 129.3 (q, $^2\mathcal{J}_{C-F}$ = 33.1 Hz, C-21), 128.8 (C-19), 127.8 (2C, C-13,14), 126.8 (C-17), 126.7 (C-12), 126.5 (C-9), 126.4 (C-15), 126.0 (q, $^3\mathcal{J}_{C-F}$ = 3.7 Hz, C-20), 124.2 (q, $^1\mathcal{J}_{C-F}$ = 270.7 Hz, C-22), 123.5 (C-5), 111.4 (C-6), 49.2 (C-7), 38.7 (C-2), 27.0 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 412.1871, $C_{25}H_{25}NOF_3$ requires 412.1883; $[\alpha]^{22}_D$ = −17.7 ° (c = 1.5, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 227 nm) indicated 95% *e.e.*: t_R (major) = 9.69 minutes, t_R (minor) = 10.36 minutes.

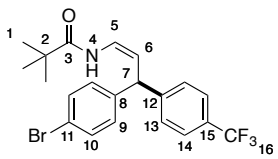
(S)-N-[(1Z)-3-(4-chlorophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **398**



Prepared according to general procedure **D** with *(Z)-N-(3-(4-chlorophenyl)allyl)pivalamide* **356** (125.9 mg, 0.5 mmol), *(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate* **367** (536 mg, 1.0 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 10% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (67 mg, 0.17 mmol, 34%).

R_F 0.40 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3444 (br., N–H), 2968, 1649 (C=O), 1617, 1486, 1463, 1324, 1165, 1118, 1068, 1015, 822; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, $\mathcal{J}$ = 7.9 Hz, 2H, H-14), 7.40–7.31 (m, 4H, H-10,13), 7.21 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-9), 6.94 (ddd, $\mathcal{J}$ = 11.1, 9.0, 2.0 Hz, 1H, H-5), 6.80 (br. d, $\mathcal{J}$ = 11.1 Hz, 1H, H-4), 5.15 (dd, $\mathcal{J}$ = 9.0, 6.5 Hz, 1H, H-6), 4.85 (d, $\mathcal{J}$ = 6.5 Hz, 1H, H-7), 0.97 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 147.3 (C-12), 141.0 (C-8), 133.3 (C-11), 129.6 (C-9), 129.5 (q, $^2\mathcal{J}_{C-F}$ = 32.4 Hz, C-15), 129.4 (C-10), 128.6 (C-13), 126.1 (q, $^3\mathcal{J}_{C-F}$ = 3.7 Hz, C-14), 124.1 (q, $^1\mathcal{J}_{C-F}$ = 271.9 Hz, C-16), 123.6 (C-5), 111.1 (C-6), 48.4 (C-7), 38.8 (C-2), 27.1 (C-1); HRMS-ESI (m/z) found $[M+H]^+$ 396.1333, $C_{21}H_{22}NOF_3Cl$ requires 396.1337; $[\alpha]^{20}_D$ = −3.1 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 233 nm) indicated 92% *e.e.*: t_R (major) = 8.05 minutes, t_R (minor) = 8.66 minutes.

(S)-N-[(1Z)-3-(4-bromophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **399**

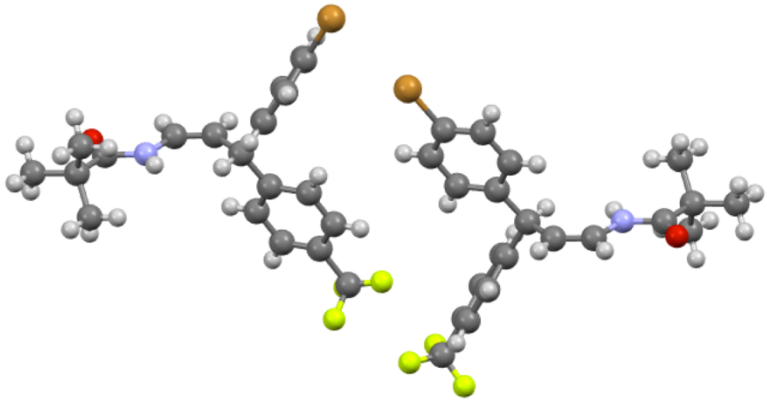


Prepared according to general procedure **D** with *(Z)-N-(3-(4-bromophenyl)allyl)pivalamide* **363** (148 mg, 0.50 mmol), *(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate* **367** (536 mg, 1.0 mmol), 2,6-di-*tert*-

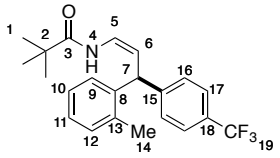
butyl pyridine (225 μL, 1.00 mmol) and Cu-BOX complex **248** (500 μL, 0.1 M, 50 μmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 10% ethyl acetate in petroleum ether 40–60, provided the title compound as an amorphous white solid (62 mg, 0.14 mmol, 28%).

R_F 0.36 (20% EtOAc in pet. ether 40–60); T_m (recrystallised from CH_2Cl_2:Hexane) 98–100 °C; IR ν_{max}/cm^{-1} (film): 3678 (br., N–H), 2972, 2909, 1649 (C=O), 1615, 1487, 1461, 1324, 1120, 1066, 1015, 801; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, $\mathcal{J}$ = 8.3 Hz, 2H, H-14), 7.48 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-10), 7.37 (d, $\mathcal{J}$ = 8.3 Hz, 2H, H-13), 7.15 (d, $\mathcal{J}$ = 8.3 Hz, 2H, H-9), 6.94 (ddd, $\mathcal{J}$ = 10.7 Hz, 8.9, 2.0 Hz, 1H, H-5), 6.80 (br. d, $\mathcal{J}$ = 10.7 Hz, 1H, H-4), 5.15 (dd, $\mathcal{J}$ = 8.9, 6.1 Hz, 1H, H-6), 4.84 (d, $\mathcal{J}$ = 6.1 Hz, 1H, H-7), 0.98 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6 (C-3), 147.2 (C-12), 141.6 (C-8), 132.4 (C-10), 130.0 (C-9), 129.6 (q, $^2\mathcal{J}_{C-F}$ = 31.9 Hz, C-15), 128.6 (C-13), 126.1 (q, $^3\mathcal{J}_{C-F}$ = 3.7 Hz, C-14), 124.1 (q, $^1\mathcal{J}_{C-F}$ = 271.4 Hz, C-16), 123.6 (C-5), 121.3 (C-11), 111.0 (C-6), 48.4 (C-7), 38.8 (C-2), 27.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 440.0826, $C_{21}H_{21}NOF_3Br$ requires 440.0831; $[\alpha]^{22}_D$ = –4.4 °(c = 1.4, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 237 nm) indicated 89% *e.e.*: t_R (major) = 8.28 minutes, t_R (minor) = 9.45 minutes; An X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre, reference number CCDC 1050909.

Crystals were grown by vial-in-vial diffusion of hexanes into a dichloromethane solution of the enamide at –18 °C. Formula $C_{21}H_{21}BrF_3NO$ and formula weight: 440.30; Temperature: 180(2) K; λ = 0.71073 Å; Space group P2(1)2(1)2(1); Cell lengths: a = 10.0251(2) Å, b = 11.4891(2) Å, c = 34.7369(2) Å; Cell angles α = 90 °, β = 90 °, γ = 90 °; Cell volume 4000.97(11) $Å^3$; Z = 8; Goodness-of-fit on F^2 = 1.021.



(S)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **403**

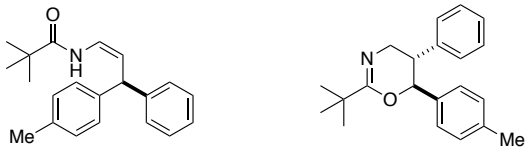


Prepared according to general procedure **D** with *(Z)-N-(3-(2-tolyl)allyl)pivalamide* **358** (116 mg, 0.50 mmol), *(4-trifluoromethylphenyl)(mesityl)iodonium hexafluorophosphate* **367** (536 mg, 1.0 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (4.3 mL). Silica column chromatography, eluting with a gradient of 0 to 10% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (49 mg, 0.13 mmol, 26%).

R_F0.44 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3428 (br., N–H), 2964, 1681, 1647 (C=O), 1484, 1461, 1322, 1163, 1120, 1066, 1016, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, $\mathcal{J}$ = 8.3 Hz, 2H, H-17), 7.35 (d, $\mathcal{J}$ = 8.3 Hz, 2H, H-16), 7.25–7.17 (m, 4H, H-9,10,11,12), 6.90 (ddd, $\mathcal{J}$ = 10.5, 9.0, 1.7 Hz, 1H, H-7), 6.77 (br. d, $\mathcal{J}$ = 10.5 Hz, 1H, H-4), 5.12 (dd, $\mathcal{J}$ = 9.0, 5.9 Hz, 1H, H-6), 5.05 (d, 5.9 Hz, 1H, H-7), 2.32 (s, 3H, H-14), 0.92 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (C-3), 147.1 (C-15), 140.1 (C-8), 136.6 (C-13), 131.3 (C-12), 129.2 (q, $^2\mathcal{J}_{C-F}$ = 33.0 Hz, C-18), 128.9 (C-14), 128.6 (C-9), 127.6 (C-11), 127.1 (C-10), 125.8 (q, $^3\mathcal{J}_{C-F}$ = 3.4 Hz, C-17), 124.2 (q, $^1\mathcal{J}_{C-F}$ = 271.9 Hz, C-19), 123.3 (C-5), 111.3 (C-6), 45.9 (C-7), 38.7 (C-2), 27.1 (C-1), 19.9 (C-14); HRMS-ESI (*m/z*) found $[M+H]^+$ 376.1878, $C_{22}H_{25}NOF_3$ requires 376.1883; $[\alpha]^{20}_D$ = –31.2 ° (c = 1.9, $CHCl_3$); HPLC analysis (IC, 20% *i*-PrOH in *n*-hexane, 1 mL/min, 202 nm) indicated >98% *e.e.*: t_R (minor) = 6.50 minutes, t_R (major) = 8.51 minutes.

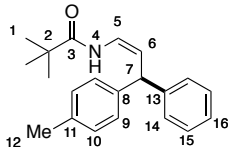
6.2.5. Oxazine products and derivatives

(S,Z)-N-(3-phenyl-3-(p-tolyl)prop-1-en-1-yl)pivalamide **405** and *(5R,6R)-2-(tert-butyl)-5-phenyl-6-(4-tolyl)-5,6-dihydro-4H-1,3-oxazine* **407**[2] – Prepared by Dr Matthieu Tissot



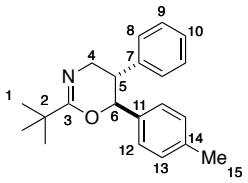
Prepared according to general procedure **D** with *(Z)-N-(3-(p-tolyl)allyl)pivalamide* **361** (116 mg, 0.50 mmol), *(mesityl)(phenyl)iodonium hexafluorophosphate* **373** (468 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL). Alumina column chromatography, eluting with a gradient of 5 to 10% diethyl ether in petroleum ether 40–60, provided the title oxazine product as a crystalline white solid (45 mg, 0.15 mmol, 29%) together with the regioisomeric enamide product an amorphous white solid (16 mg, 0.05 mmol, 10%).

(S,Z)-N-(3-phenyl-3-(p-tolyl)prop-1-en-1-yl)pivalamide **405**



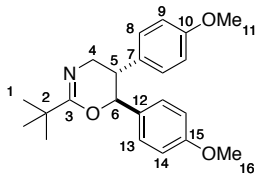
IR ν_{max}/cm^{-1} (film): 3427 (br., N–H), 2962, 1651 (C=O), 1484, 1278, 1177, 801, 747, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.27 (m, 4H. H-14,15), 7.25–7.13 (m, 5H, H-9,10,16), 6.89–6.87 (m, 2H, H-4,5), 5.22 (dd, $\mathcal{J}$ = 8.4, 5.8 Hz, 1H, H-6), 4.79 (d, $\mathcal{J}$ = 5.8 Hz, 1H, H-7), 2.32 (s, 3H, H-12), 0.93 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.5 (C-3), 143.9 (C-13), 140.6 (C-8), 136.7 (C-11), 129.8 (C-10), 129.1 (C-15), 128.3 (C-14), 128.2 (C-9), 126.9 (C-16), 122.7 (C-5), 113.0 (C-6), 49.1 (C-7), 27.1 (C-2), 21.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 308.2009, $C_{21}H_{26}NO$ requires 308.2012. $[\alpha]^{26}_D$ = –10.8 º (c = 1.0, $CHCl_3$), calculated with sample *e.e.* of 94%; HPLC analysis (OD, 1% *i*-PrOH in *n*-hexane, 1 mL/min, 236 nm) indicated 96% *e.e.*: t_R (major) = 13.13 minutes, t_R (minor) = 14.09 minutes.

(5R,6R)-2-(tert-butyl)-5-phenyl-6-(4-tolyl)-5,6-dihydro-4H-1,3-oxazine **407**[157]



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.15 (m, 3H, H-10,13), 7.04–7.00 (m, 4H, H-8,9), 6.97 (d, $\mathcal{J}$ = 8.1 Hz, 2H, H-12), 5.10 (d, $\mathcal{J}$ = 10.0 Hz, 1H, H-6), 3.74–3.65 (m, 2H, H-4), 2.91 (app. td, $\mathcal{J}$ = 9.5, 6.7 Hz, 1H, H-5), 2.28 (s, 3H, H-15), 1.27 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6 (C-3), 139.4 (C-7), 137.7 (C-14), 136.4 (C-11), 128.9 (C-9), 128.6 (C-13), 128.3 (C-8), 127.1 (C-10), 126.7 (C-12), 81.2 (C-6), 49.8 (C-4), 45.6 (C-5), 37.6 (C-2), 28.0 (C-1), 21.2 (C-15); $[\alpha]^{26}_D$ = +92.9 º (c = 1.0, $CHCl_3$); HPLC analysis (OD, 1% *i*-PrOH in *n*-hexane, 1 mL/min, 202 nm) indicated 98% *e.e.*: t_R (major) = 6.94 minutes, t_R (minor) = 8.34 minutes. Experimental data in agreement with previous literature report.[157]

(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **410**

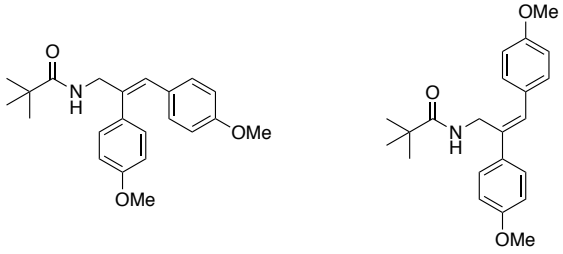


Prepared according to general procedure **D** with *(Z)-N-(3-(4-methoxyphenyl)allyl)pivalamide* **360** (124 mg, 0.50 mmol), *(mesityl)(4-methoxyphenyl)iodonium hexafluorophosphate* **374** (498 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL) with stirring at 40 ºC for 30 hours. Alumina column chromatography, eluting with 5% ethyl

acetate in petroleum ether 40–60, provided the title compound as a white solid (139 mg, 0.39 mmol, 79%).

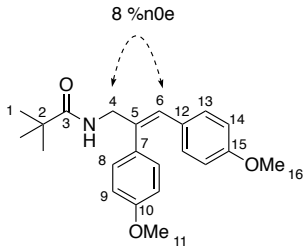
T_m 120–125 °C; IR ν_{max}/cm^{-1} (film): 2960, 2917, 2837, 1667, 1613, 1512, 1245, 1177, 1136, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.97 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-13), 6.88 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-8), 6.74 (app. d, $\mathcal{J}$ = 8.5 Hz, 4H, H-9,14), 5.00 (d, $\mathcal{J}$ = 10.1 Hz, 1H, H-6), 3.75 (s, 3H, H-16), 3.74 (s, 3H, H-11), 3.67–3.57 (m, 2H, H-4), 2.81 (app. td, $\mathcal{J}$ = 9.9, 6.4 Hz, 1H, H-5), 1.24 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3 (C-3), 159.2 (C-15), 158.5 (C-10), 131.8 (C-12), 131.4 (C-7), 129.2 (C-8), 128.0 (C-13), 114.1 (C-9), 113.6 (C-14), 81.1 (C-6), 55.3 (2C, C-11,16), 50.1 (C-4), 44.9 (C-5), 37.6 (C-2), 28.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 354.2065, $C_{22}H_{28}NO_3$ requires 354.2064; $[\alpha]^{29}_D$ = +92.4 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 238 nm) indicated 82% *e.e.*: t_R (major) = 12.23 minutes, t_R (minor) = 14.45 minutes.

(E/Z)-N-(2,3-bis(4-methoxyphenyl)allyl)pivalamide **413**



Prepared according to general procedure **D** with *(Z)-N-(3-(4-methoxyphenyl)allyl)pivalamide* **360** (24.7 mg, 0.10 mmol), *(mesityl)(4-methoxyphenyl)iodonium hexafluorophosphate* **374** (105 mg, 0.20 mmol), 2,6-di-*tert*-butyl pyridine (45 µL, 0.20 mmol) and Cu-BOX complex **248** (100 µL, 0.1 M, 5 µmol) in dichloromethane (1.85 mL). Silica column chromatography, eluting with 10 to 20% ethyl acetate in petroleum ether 40–60, provided the *Z*- isomer of the title compound as an amorphous white solid (3.6 mg, 10 µmol, 10%) and the *E*- isomer of the title compound as a colourless oil (5.8 mg, 16 µmol, 16%).

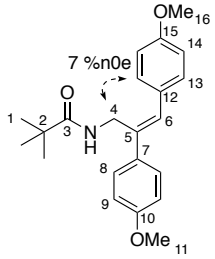
(E)-N-(2,3-bis(4-methoxyphenyl)allyl)pivalamide **413a**



R_F 0.38 (50% EtOAc in pet. ether 40-60); IR ν_{max}/cm^{-1} (film): 3353 (br., N–H), 2958, 2837, 1740, 1644 (C=O), 1609, 1509, 1463, 1288, 1246, 1176; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-8), 6.93 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-13), 6.85 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-9), 6.66 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-14), 6.47 (s, 1H, H-6), 5.62 (br. t, $\mathcal{J}$ = 5.3 Hz, 1H, N–H), 4.24 (dd, $\mathcal{J}$ = 5.6, 0.7 Hz, 2H, H-4), 3.81 (s, 3H, H-11/16), 3.74 (s, 3H, H-11/16), 1.08 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.2 (C-3), 159.0 (C-

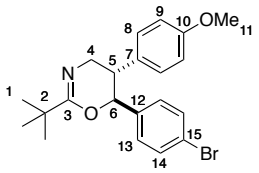
10), 158.5 (C-15), 136.5 (C-6), 130.9 (C-12), 130.6 (C-13), 130.1 (C-8), 129.3 (C-7), 126.9 (C-6), 114.3 (C-9), 113.5 (C-14), 55.4 (C-11), 55.3 (C-16), 47.3 (C-4), 38.8 (C-2), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 354.2063, $C_{22}H_{28}NO_3$ requires 354.2064.

(Z)-N-(2,3-bis(4-methoxyphenyl)allyl)pivalamide **413b**



R_F 0.50 (50% EtOAc in pet. ether 40-60); IR ν_{max}/cm^{-1} (film): 3306 (br., N–H), 2959, 1624 (C=O), 1610, 1544, 1515, 1465, 1253, 1178, 1033; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-8), 7.27 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-13), 6.93–6.88 (m, 4H, H-9,14), 6.84 (s, 1H, H-6), 5.46 (br. t, $\mathcal{J}$ = 4.8 Hz, 1H, N–H), 4.52 (d, $\mathcal{J}$ = 4.8 Hz, 2H, H-4), 3.83 (s, 6H, H-11,16), 1.04 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.3 (C-3), 159.4 (C-10), 158.9 (C-15), 136.1 (C-5), 133.0 (C-12), 130.2 (C-13), 129.6 (C-7), 129.4 (C-6), 127.8 (C-8), 114.1 (2C, C-9,13), 55.5 (2C, C-11,16), 39.1 (C-2), 38.7 (C-4), 27.6 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 354.2062, $C_{22}H_{28}NO_3$ requires 354.2064.

(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-bromophenyl)-5,6-dihydro-4H-1,3-oxazine **412**

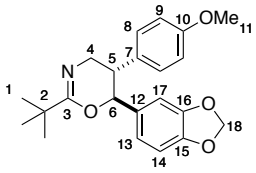


Prepared according to general procedure **D** with *(Z)-N-(3-(4-bromophenyl)allyl)pivalamide* **363** (148 mg, 0.50 mmol), *(mesityl)(4-methoxyphenyl)iodonium hexafluorophosphate* **374** (498 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL) with stirring for 43 hours. Alumina column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as a white crystalline solid (129 mg, 0.32 mmol, 64%).

T_m 148–152 °C; IR ν_{max}/cm^{-1} (film): 2960, 2929, 1669, 1611, 1512, 1489, 1423, 1245, 1136, 1033; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.33 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-14), 6.89 (d, $\mathcal{J}$ = 8.5 Hz, 2H, H-13), 6.87 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-8), 6.76 (d, $\mathcal{J}$ = 8.8 Hz, 2H, H-9), 4.98 (d, $\mathcal{J}$ = 10.2 Hz, 1H, H-6), 3.75 (s, 3H, H-11), 3.60–3.67 (m, 2H, H-4), 2.75 (app. td, $\mathcal{J}$ = 9.8, 6.4 Hz, 1H, H-5), 1.23 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.8 (C-3), 158.8 (C-10), 138.7 (C-12), 131.3 (C-14), 130.8 (C-7), 129.3 (C-8), 128.5 (C-13), 121.9 (C-15), 114.2 (C-9), 80.8 (C-6), 55.3 (C-11), 49.9 (C-4), 50.0 (C-5), 37.6 (C-2), 28.0 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 402.1063, $C_{21}H_{25}BrNO_2$ requires 402.1063; $[\alpha]^{29}_D$ = +97.3 ° (c = 1.0,

$CHCl_3$), calculated with sample *e.e.* of 79%; HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 227 nm) indicated 91% *e.e.*: t_R (major) = 8.56 minutes, t_R (minor) = 9.65 minutes.

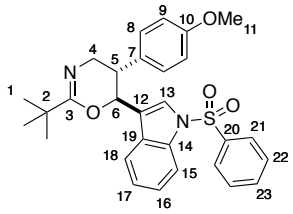
(5S,6S)-6-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butyl)-5-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **414**



Prepared according to general procedure **D** with *(Z)-N-(3-(benzo[d][1,3]dioxol-5-yl)allyl)pivalamide* **365** (131 mg, 0.50 mmol), *(mesityl)(4-methoxyphenyl)iodonium hexafluorophosphate* **374** (498 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL) with stirring for 15 hours. Alumina column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60, provided the title compound as a white solid (148 mg, 0.40 mmol, 80%).

T_m 145–146 °C; IR ν_{max}/cm^{-1} (film): 2964, 1669, 1613, 1514, 1491, 1443, 1247, 1179, 1140, 1037; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.89 (d, J = 8.7 Hz, 2H, H-8), 6.75 (d, J = 8.7 Hz, 2H, H-9), 6.62 (d, J = 1.6 Hz, 1H, H-17), 6.60 (d, J = 8.0 Hz, 1H, H-14), 6.44 (dd, J = 8.0, 1.6 Hz, 2H, H-13), 5.91 (d, J = 2.7 Hz, 1H, H-18a), 5.90 (d, J = 2.7 Hz, 1H, H-18b), 4.94 (d, J = 10.2 Hz, 1H, H-6), 3.74 (s, 3H, H-11), 3.66–3.56 (m, 2H, H-4), 2.78 (app. td, J = 10.1, 5.9 Hz, 1H, H-5), 1.22 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (C-3), 158.6 (C-10), 147.6 (C-16), 147.2 (C-15), 133.5 (C-12), 131.2 (C-7), 129.2 (C-8), 120.8 (C-13), 114.1 (C-9), 107.9 (C-14), 107.0 (C-17), 101.1 (C-18), 81.3 (C-6), 55.3 (C-11), 50.1 (C-4), 44.9 (C-5), 37.5 (C-2), 28.0 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 368.1858, $C_{22}H_{26}NO_4$ requires 368.1856; $[\alpha]^{24.}{}_D$ = +140.4 ° (c = 1.0, $CHCl_3$); HPLC analysis (AD-H, 1% *i*-PrOH in *n*-hexane, 1 mL/min, 231 nm) indicated 89% *e.e.*: t_R (major) = 22.46 minutes, t_R (minor) = 29.61 minutes.

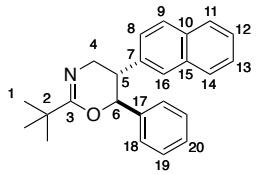
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(1-(phenylsulfonyl)-1H-indol-3-yl)-5,6-dihydro-4H-1,3-oxazine **415**



Prepared according to general procedure **D** with *(Z)-N-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)allyl)pivalamide* **364** (198 mg, 0.50 mmol), *(mesityl)(4-methoxyphenyl)iodonium hexafluorophosphate* **374** (498 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL) with stirring for 2.5 hours. Alumina column chromatography, eluting with a gradient of 10 to 85% diethyl ether in petroleum ether 40–60, provided the title compound as an off-white solid (153 mg, 0.31 mmol, 61%).

T_m 72–76 °C; IR ν_{max}/cm^{-1} (film): 2960, 2925, 1669, 1611, 1510, 1449, 1368, 1245, 1177, 1123; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J = 8.3 Hz, 1H, H-15), 7.55 (d, J = 7.7 Hz, 1H, H-18), 7.51–7.47 (m, 3H, H-21,23), 7.35–7.31 (m, 2H, H-22), 7.28 (app. t, J = 8.3 Hz, 1H, H-17), 7.24 (s, 1H, H-13), 7.21 (app. t, J = 7.6 Hz, 1H, H-16), 6.88 (d, J = 8.7 Hz, 2H, H-8), 6.70 (d, J = 8.7 Hz, 2H, H-9), 5.29 (d, J = 10.4 Hz, 1H, H-6), 3.77 (s, 3H, H-11), 3.71 (dd, J = 16.3, 5.2 Hz, 1H, H-4a), 3.60 (dd, J = 16.3, 10.7 Hz, 1H, H-4b), 3.22 (app. td, J = 10.7, 5.2 Hz, 1H, H-5), 1.21 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9 (C-3), 158.6 (C-10), 137.9 (C-20), 135.3 (C-14), 133.8 (C-23), 131.6 (C-7), 129.3 (C-22), 129.0 (C-19), 128.8 (C-8), 126.7 (C-21), 125.1 (C-13), 125.0 (C-17), 123.5 (C-16), 120.7 (C-18), 120.5 (C-12), 114.3 (C-9), 113.8 (C-15), 75.3 (C-6), 55.4 (C-11), 50.5 (C-4), 42.2 (C-5), 37.7 (C-2), 28.0 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 503.1988, $C_{29}H_{31}SN_2O_4$ requires 503.1999; $[\alpha]^{24}_D$ = +49.6 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 222 nm) indicated 91% *e.e.*: t_R (major) = 23.32 minutes, t_R (minor) = 35.79 minutes.

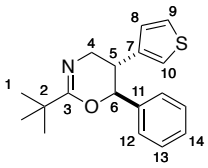
(5S,6S)-2-(tert-butyl)-5-(naphthalen-2-yl)-6-phenyl-5,6-dihydro-4H-1,3-oxazine **423**



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (109 mg, 0.50 mmol), *(2-napthyl)(mesityl)iodonium hexafluorophosphate* **375** (518 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL). Alumina column chromatography, eluting with a gradient of 5 to 50% diethyl ether in petroleum ether 40–60, provided the title compound as a yellow solid (55 mg, 0.19 mmol, 37%).

T_m 130–133 °C; IR ν_{max}/cm^{-1} (film): 2968, 2917, 1665, 1600, 1478, 1455, 1391, 1268, 1138, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.67 (m, 3H, H-9,11,14), 7.49 (app. br. s, 1H, H-16), 7.46–7.39 (m, 2H, H-12,13), 7.19–7.15 (m, 3H, H-19,20), 7.12–7.05 (m, 3H, H-8,18), 5.25 (d, J = 9.8 Hz, 1H, H-6), 3.84–3.70 (m, 2H, H-4), 3.08 (app. td, J = 10.0, 5.4 Hz, 1H, H-5), 1.28 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (C-3), 139.5 (C-17), 136.9 (C-7), 133.5 (C-15), 132.6 (C-10), 128.30 (C-9), 128.26 (C-19), 128.0 (C-20), 127.8 (C-11), 127.7 (C-14), 127.1 (C-16), 126.7 (C-18) 126.5 (C-8), 126.2 (C-12/13), 125.8 (C-12/13), 81.1 (C-6), 49.8 (C-4), 45.8 (C-5), 37.7 (C-2), 28.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 344.2009, $C_{24}H_{26}NO$ requires 344.2009; $[\alpha]^{24}_D$ = +120.7 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 215 nm) indicated 92% *e.e.*: t_R (major) = 5.80 minutes, t_R (minor) = 6.21 minutes.

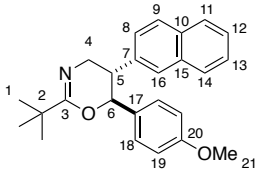
(5S,6S)-2-(tert-butyl)-6-phenyl-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **424**[2]



Prepared according to general procedure **D** with *(Z)-N-(3-phenylallyl)pivalamide* **315** (109 mg, 0.50 mmol), *(mesityl)(3-thiophenyl)iodonium hexafluorophosphate* **376** (474 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (225 µL, 1.00 mmol) and Cu-BOX complex **248** (500 µL, 0.1 M, 50 µmol) in dichloromethane (9.3 mL). Alumina column chromatography, eluting with a gradient of 5 to 20% diethyl ether in petroleum ether 40–60, provided the title compound as a colourless oil (47 mg, 0.16 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.25 (m, 3H, H-13,14), 7.20 (dd, $\mathcal{J}$ = 5.0, 2.9 Hz, 1H, H-8), 7.09–7.06 (m, 2H, H-12), 6.84 (dd, $\mathcal{J}$ = 2.9, 1.1 Hz, 1H, H-10), 6.72 (dd, $\mathcal{J}$ = 5.0, 1.1 Hz, 1H, H-9), 5.05 (d, $\mathcal{J}$ = 9.4 Hz, 1H, H-6), 3.69–3.67 (m, 2H, H-4), 3.08 (app. td, $\mathcal{J}$ = 8.7, 7.1 Hz, 1H, H-5), 1.26 (s, 9H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1 (C-3), 139.75 (C-7), 139.73 (C-11), 128.2 (C-13), 128.1 (C-14), 127.2 (C-9), 126.5 (C-12), 125.7 (C-8), 121.8 (C-10), 81.2 (C-6), 49.0 (C-4), 41.1 (C-5), 37.6 (C-2), 28.0 (C-1); $[\alpha]^{26}_D$ = +57.1 ^{o} (c = 1.0, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 248 nm) indicated 92% *e.e.*: t_R (major) = 6.10 minutes, t_R (minor) = 7.51 minutes. Experimental data in agreement with previous literature report.[2]

(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(naphthalen-2-yl)-5,6-dihydro-4H-1,3-oxazine **425**

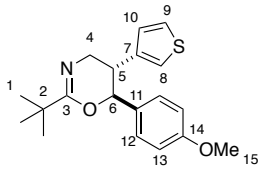


Prepared according to general procedure **D** with *(Z)-N-(3-(4-methoxyphenyl)allyl)pivalamide* **360** (49.4 mg, 0.20 mmol), *(2-napthyl)(mesityl)iodonium hexafluorophosphate* **375** (218 mg, 0.40 mmol), 2,6-di-*tert*-butyl pyridine (90 µL, 0.40 mmol) and Cu-BOX complex **248** (200 µL, 0.1 M, 20 µmol) in dichloromethane (3.7 mL) with stirring for 20 hours. Alumina column chromatography, eluting with a gradient of 2.5 to 5% ethyl acetate in petroleum ether 40–60, provided the title compound as a colourless oil (31.2 mg, 0.08 mmol, 42%).

R_F 0.21 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2959, 2928, 1770, 1614, 1515, 1480, 1461, 1249, 1137, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (dd, $\mathcal{J}$ = 7.6, 2.2 Hz, 1H, H-9), 7.73–7.67 (m, 2H, H-11,14), 7.49 (app. br. s, 1H, H-16), 7.46–7.39 (m, 2H, H-12,13), 7.11 (dd, $\mathcal{J}$ = 7.6, 1.5 Hz, 1H, H-8), 7.02 (d, $\mathcal{J}$ = 8.7, 2H, H-18), 6.70 (d, $\mathcal{J}$ = 8.7 Hz, 2H, H-19), 5.20 (d, $\mathcal{J}$ = 10.0 Hz, 1H, H-6), 3.79–3.72 (m, 2H, H-4), 3.70 (s, 3H, H-21), 3.06 (app. td, $\mathcal{J}$ = 10.0, 5.8 Hz, 1H, H-5), 1.26 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.4 (C-3), 159.3 (C-20), 137.1 (C-7), 133.5 (C-15), 132.6 (C-10), 131.6

(C-17), 128.3 (C-9), 128.0 (C-18), 127.8 (C-11), 127.7 (C-14), 127.1 (C-16), 126.5 (C-8), 126.2 (C-12/13), 125.8 (C-12/13), 113.7 (C-19), 80.8 (C-6), 55.2 (C-21), 50.1 (C-4), 45.8 (C-5), 37.6 (C-2), 28.1 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 374.2115, $C_{25}H_{28}NO_2$ requires 374.2115; $[\alpha]^{25}_D$ = +83.0 ° (c = 0.5, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 225 nm) indicated 52% *e.e.*: t_R (major) = 6.96 minutes, t_R (minor) = 7.55 minutes.

(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **426**



Prepared according to general procedure **D** with *(Z)-N-(3-(4-methoxyphenyl)allyl)pivalamide* **360** (49.4 mg, 0.20 mmol), *(mesityl)(3-thiophenyl)iodonium hexafluorophosphate* **376** (180 mg, 0.40 mmol), 2,6-di-*tert*-butyl pyridine (90 µL, 0.40 mmol) and Cu-BOX complex **248** (200 µL, 0.1 M, 20 µmol) in dichloromethane (3.7 mL) with stirring for 20 hours. Alumina column chromatography, eluting with a gradient of 2.5 to 5% ethyl acetate in petroleum ether 40–60, provided the title compound as an inseparable 5:1 mixture of diasteroiosomers and as a yellow oil (34.7 mg, 0.11 mmol, 55%).

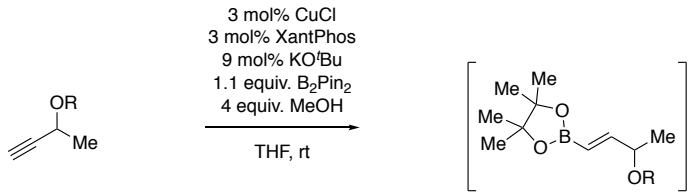
R_F 0.17 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2958, 2925, 1670, 1614, 1515, 1480, 1461, 1248, 1136, 1030; *Major diastereoisomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.18 (dd, J = 5.0, 3.0 Hz, 1H, H-10), 7.00 (d, J = 8.7 Hz, 2H, H-12), 6.81 (d, J = 3.0 Hz, 1H, H-8), 6.78 (d, J = 8.7 Hz, 2H, H-13), 6.70 (d, J = 5.0 Hz, 1H, H-9), 4.98 (d, 1H, J = 9.6 Hz, H-6), 3.77 (s, 3H, H-15), 3.71–3.57 (m, 2H, H-4), 3.05 (app. td, J = 9.6, 5.7 Hz, 1H, H-5), 1.23 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3 (C-3), 159.4 (C-14), 139.9 (C-7), 131.9 (C-11), 127.8 (C-12), 127.2 (C-9), 125.7 (C-8), 121.7 (C-10), 113.7 (C-12), 80.9 (C-6), 55.3 (C-15), 49.3 (C-4), 41.2 (C-5), 37.6 (C-2), 28.0 (C-1); *Minor diasteroisomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (dd, J = 5.0, 3.1 Hz, 1H, H-10), 6.95 (d, J = 8.6 Hz, 2H, H-12), 6.90 (d, J = 3.1 Hz, 1H, H-8), 6.80 (d, J = 8.6 Hz, 2H, H-13), 6.72 (d, J = 5.0 Hz, 1H, H-9), 5.17 (d, 1H, J = 10.0 Hz, H-6), 3.77 (s, 3H, H-15), 3.71–3.57 (m, 2H, H-4), 2.82 (app. td, J = 10.0, 5.3 Hz, 1H, H-5), 1.24 (s, 9H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.9 (C-3), 158.7 (C-14), 141.0 (C-7), 131.6 (C-11), 129.2 (C-12), 125.9 (C-9), 125.5 (C-8), 122.0 (C-10), 114.2 (C-12), 77.7 (C-6), 55.3 (C-15), 50.0 (C-4), 44.5 (C-5), 37.6 (C-2), 28.0 (C-1); HRMS-ESI (*m/z*) found $[M+H]^+$ 330.1524, $C_{19}H_{24}NSO_2$ requires 330.1522; $[\alpha]^{25}_D$ = +31.3 ° (c = 1.0, $CHCl_3$); HPLC analysis (IC, 5% *i*-PrOH in *n*-hexane, 1 mL/min, 215 nm) indicated: major diasteroisomer – 63% *e.e.*: t_R (major) = 7.60 minutes, t_R (minor) = 8.85 minutes; minor diasteroisomer – 6% *e.e.*: t_R (minor) = 8.27 minutes, t_R (major) = 12.78 minutes.

6.3 Studies Towards the Total Synthesis of (−)-Lyngbyaloside B

6.3.1. General procedures

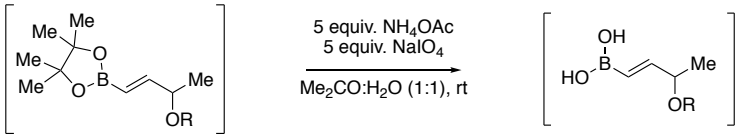
General procedure ***E***

Three step synthesis of alkenyl iodonium salts via a borylation strategy:

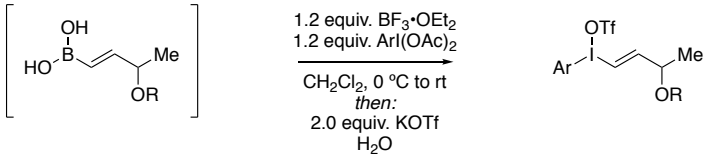


Adapted from procedures reported by Wong et al. and Gaunt et al.; all quantities given with respect to initial alkyne loading.[158,220]

E1: An oven-dried Schlenk flask was charged with copper (I) chloride (3 mol%), XantPhos (3 mol%) and potassium *tert*-butoxide (9 mol%) and back-filled three times with nitrogen gas. The resulting mixture was suspended in the stated volume of tetrahydrofuran and stirred for 30 minutes before the addition of a solution of bis(pincolato)diboron (1.1 equiv. in the stated volume of THF) with stirring for a further 15 minutes. A solution of alkyne (1.0 equiv.) in the stated volume of tetrahydrofuran was added to the resulting borylation mixture followed by a portion of methanol (4.0 equiv.) with the reaction mixture then allowed to stir for 15 hours. The resulting grey suspension was then filtered through a pad of celite™, eluting with diethyl ether, and concentrated *in vacuo* to give the corresponding vinyl boronic ester for immediate consumption in the following step.



E2: To a stirred suspension of vinyl boronic acid in a 1:1 mixture of acetone/water was added ammonium acetate (5.0 equiv.) and sodium *meta*-periodate (5.0 equiv.). The resulting green reaction mixture was vigorously stirred for 18 hours before the acetone was removed *in vacuo*. The residual aqueous slurry was extracted with three portions of ethyl acetate and the organics combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude intermediate vinyl boronic acid for immediate consumption in the following step.

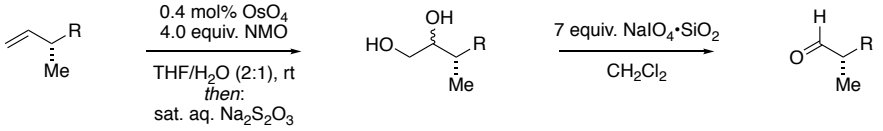


E3: The boronic acid residue was dissolved in a stated volume of dichloromethane and cooled to 0 °C before undergoing subsquent dropwise additions of boron trifluoride diethyl etherate (1.2 equiv.) and a

solution of iodoarene diacetate (1.2 equiv.) in a stated volume of dichloromethane. The resulting reaction mixture was warmed to room temperature and was stirred for a further two hours before quenching with the given quantity of water and a portion of potassium trifluoromethanesulfonate (2.0 equiv.). The biphasic mixture was vigorously stirred for a further 15 minutes, the phases separated, and the aqueous layer extracted with three portions of dichloromethane. The combined organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude iodonium salt was purified by silica column chromatography, eluting with a gradient of acetone in dichloromethane, and subsequently precipitated to furnish the desired alkenyl iodonium salt.

General Procedure ***F***

Two-step dihydroxylation and periodate cleavage of alkenes to give a-chiral aldehydes with high levels of stereoretention:



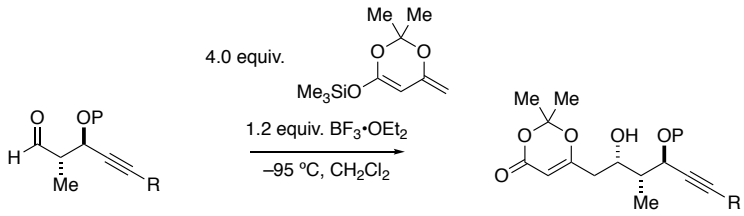
All quantities given with respect to the initial alkene loading

F1: NMO (50 wt% in H_2O, 4.0 equiv.) and OsO_4 (2.5 wt% in ^{t}BuOH, 0.4 mol%) were added to a stirred suspension of alkene (1.0 equiv.) in tetrahydrofuran and water (2:1, 0.03 M). The resulting solution was stirred for the stated time before quenching with the stated volumes of sat. aq. $Na_2S_2O_3$ solution and ethyl acetate. The phases were separated and the aqueous phase extracted with further portions of ethyl acetate. The organic fractions were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to furnish the intermediate diol as a mixture of diastereoisomers.

F2: The crude diol mixture was re-dissolved in the stated volume of dichloromethane and silica-supported sodium *meta*-periodate[iv] (approx. 15 wt% $NaIO_4$, 7.0 equiv.) was added in one portion. The resulting suspension was stirred for 15 minutes then filtered, washing the silica cake with 50% diethyl ether in dichloromethane. The filtrate was concentrated *in vacuo* and the residue purified by silica column chromatography to furnish the title compound for immediate consumption.

General Procedure ***G***

Vinylogous Mukaiyama aldol reaction:



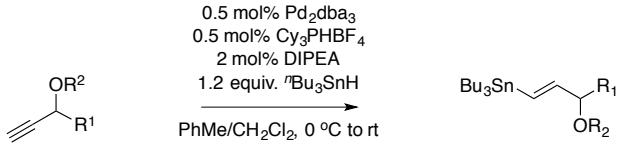
[iv] Silica-supported sodium *meta*-periodate was prepared as follows: Silica gel (20 g, Merck Kieselgel 60) was added to a suspension of $NaIO_4$ (5.14 g, 24 mmol) in water (10 mL) and the vessel shaken vigorously for 10 minutes to give the solid supported reagent as a free-flowing white powder.

All quantities given with respect to the initial aldehyde loading

Adapted from a procedure reported by Fuwa et al.[178] Solutions of *((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane* (4.0 equiv.) in dichloromethane and boron trifluoride diethyl etherate (1.2 equiv.) in dichloromethane were added sequentially at −95 °C ($PhMe/N_{2(l)}$) to a solution of the aldehyde (1.0 equiv.) in dichloromethane. The reaction mixture was maintained at −95 °C for a further 40 minutes then quenched by the addition of the stated volumes of triethylamine and sat. aq. $NaHCO_3$. The resulting product mixture was then allowed to warm to 0 °C then to room temperature with vigorous stirring. The crude biphasic reaction mixture was separated and the aqueous layer extracted with portions of dichloromethane. The organic fractions were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica column chromatography to furnish the desired aldol adduct.

General Procedure ***H***

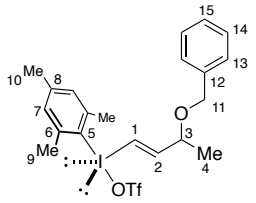
Regio- and steroselective hydrostannylation of alkynes to give terminal, E-vinyl stannanes



Adapted from a procedure reported by Chong et al, all quantities given with respect to alkyne loading.[206] Freshly distilled di*iso*propylethylamine (2 mol%) was added to a solution of Pd_2dba_3 (0.5 mol%) and tricyclohexylphosphonium tetrafluoroborate (2 mol%) in the stated volume of the stated solvent. The resulting catalytic solution was stirred for fifteen minutes before cooling to 0 °C. To this cooled solution was added the alkyne substrate (1.0 equiv.) in the stated volume of solvent, followed by the dropwise addition of tributyltin hydride (1.2 equiv.) in the stated volume of solvent over a five-minute period. The resulting solution was warmed to room temperature and was stirred for two hours. The reaction mixture was then concentrated onto silica gel and purified by silica column chromatography to furnish the desired vinyl stannane.

6.3.2. Model coupling studies

(E)-(3-(benzyloxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate **481**



Prepared according to general procedure **E** on a 3.5 mmol scale:

Step E1 was performed with CuCl (12.0 mg, 0.113 mmol), XantPhos (70.0 mg, 0.113 mmol) and KO^{t}Bu (40.4 mg, 0.360 mmol) in THF (6.4 mL), B_2Pin_2 (1.12 g, 4.13 mmol) in THF (3.2 mL), *((but-3-yn-2-yloxy)methyl)benzene* **539** (560 mg, 3.50 mmol), and methanol (320 µL, 15.0 mmol) to furnish the intermediate pinicolatoboronic ester *(E)-2-(3-(benzyloxy)but-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* as a yellow oil for direct consumption in step E2.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38–7.29 (m, 5H, H-13,14,15), 6.55 (dd, J = 18.2, 6.4 Hz, 1H, H-2), 5.64 (dd, J = 18.2, 0.9 Hz, 1H, H-1), 4.58 (d, J = 12.0 Hz, 1H, H-11a), 4.37 (d, J = 12.0 Hz, 1H, H-11b), 3.98 (app. qnd, J = 6.4, 0.9 Hz, 1H, H-3). H-4 obscured by pinacol methyl groups.

Step E2 was performed with ammonium acetate (1.35 g, 17.5 mmol) and sodium *meta*-periodate (3.70 g, 17.5 mmol) in acetone (20 mL) and water (20 mL) to furnish a crude yellow oil containing the intermediate boronic acid *(E)-(3-(benzyloxy)but-1-en-1-yl)boronic acid* for immediate use in step E3.

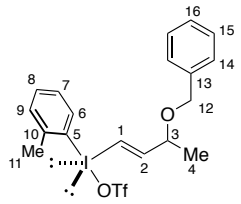
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.94 (dd, J = 17.8, 6.3 Hz, 1H, H-2), 5.80 (dd, J = 17.8, 1.0 Hz, 1H, H-1), 4.63 (d, J = 12.0 Hz, 1H, H-11a), 4.46 (d, J = 12.0 Hz, 1H, H-11b), 4.14–4.07 (m, 1H, H-3), 1.36 (d, J = 6.5 Hz, 3H, H-4). Phenyl resonances obscured by impurities.

Step E3 was performed in dichloromethane (28 mL) with boron trifluoride diethyl etherate (0.52 mL, 4.20 mmol) and mesityl iodonium diacetate (1.53 g, 4.20 mmol) in a solution of dichloromethane (14 mL). The reaction was quenched with the addition of potassium trifluoromethanesulfonate (1.40 g, 7.00 mmol) and water (140 mL) and purified by silica column chromatography, eluting with 0–50% acetone in dichloromethane. The resulting purified iodonium salt was precipitated with diethyl ether to furnish the title compound as an amorphous off-white solid (1.18 g, 2.13 mmol, 61% over three steps).

IR ν_{max}/cm^{-1} (film): 3034, 2987, 2920, 1591 (C=C), 1455, 1405, 1248, 1225, 1156, 1080, 1059, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35–7.26 (m, 3H, H-14,15), 7.25–7.20 (m, 2H, H-13), 7.10 (s, 2H, H-7), 6.86 (dd, J = 14.1, 0.7 Hz, 1H, H-1), 6.13 (dd, J = 14.1, 6.6 Hz, 1H, H-2), 4.43 (d, J = 11.8 Hz, 1H, H-11a), 4.39 (d, J = 11.8 Hz, 1H, H-11b), 4.15 (app. qn, J = 6.4 Hz, 1H, H-3), 2.57 (s, 6H, H-9), 2.36 (s, 3H, H-10), 1.23 (d, J = 6.5 Hz, 3H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.1 (C-2), 144.6 (C-8), 142.9 (C-6) 137.5 (C-12), 130.4 (C-7), 128.6 (C-14), 128.0 (C-15), 127.8 (C-13), 120.3 (q, ^1J = 313.3 Hz, C-Tf), 116.7 (C-5), 99.4 (C-1), 76.1 (C-3), 71.2 (C-11), 30.0 (C-9), 21.2 (C-10), 20.7 (C-

4); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −79.2; HRMS-ESI (*m/z*) found $[M–OTf]^+$ 407.0866, $C_{20}H_{24}OI$ requires 407.0866.

(E)-(3-(benzyloxy)but-1-en-1-yl)(o-tolyl)iodonium trifluoromethanesulfonate **482**

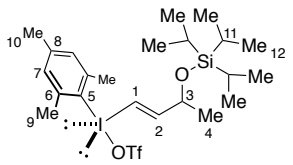


Prepared according to general procedure **E** on a 3.5 mmol scale. Steps E1 and E2 were performed analogously to the previous procedure.

Step E3 was performed in dichloromethane (28 mL) with boron trifluoride diethyl etherate (520 µL, 4.20 mmol) and *ortho*-tolyl iodonium diacetate (1.41 g, 4.20 mmol) in a solution of dichloromethane (14 mL). The reaction was quenched with the addition of potassium trifluoromethanesulfonate (1.40 g, 7.00 mmol) and water (140 mL) and purified by silica column chromatography, eluting with 0–50% acetone in dichloromethane. The resulting purified iodonium salt was precipitated with diethyl ether to furnish the title compound as an amorphous off-white solid (0.90 g, 1.61 mmol, 46% over three steps).

IR ν_{max}/cm^{-1} (film): 3062, 2982, 2923, 1603 (C=C), 1469, 1455, 1272, 1238, 1223, 1154, 1104, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, $\mathcal{J}$ = 7.9 Hz, 1H, H-6), 7.56 (app. t, $\mathcal{J}$ = 7.4 Hz, 1H, H-8), 7.49 (d, $\mathcal{J}$ = 6.9 Hz, 1H, H-9), 7.33–7.26 (m, 3H, H-15,16), 7.25–7.22 (m, 3H, H-7,14), 6.93 (d, $\mathcal{J}$ = 13.9 Hz, 1H, H-1), 6.44 (dd, $\mathcal{J}$ = 13.9, 6.2 Hz, 1H, H-2), 4.46 (d, $\mathcal{J}$ = 11.8 Hz, 1H, H-12a), 4.41 (d, $\mathcal{J}$ = 11.8 Hz, 1H, H-12b), 4.16 (qd, $\mathcal{J}$ = 6.5, 6.2 Hz, 1H, H-3), 2.59 (s, 3H, H-11), 1.25 (d, $\mathcal{J}$ = 6.5 Hz, 3H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 150.0 (C-2), 141.9 (C-10), 138.4 (C-6), 137.6 (C-13), 133.7 (C-8), 132.0 (C-9), 129.8 (C-7), 128.6 (C-15), 128.0 (C-16), 127.8 (C-14), 120.3 (q, $^1\mathcal{J}$ = 319.9 Hz, C-Tf), 115.4 (C-5), 100.1 (C-1), 76.1 (C-3), 71.2 (C-12), 25.6 (C-11), 20.5 (C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −79.2; HRMS-ESI (*m/z*) found $[M–OTf]^+$ 379.0546, $C_{18}H_{20}OI$ requires 379.0553.

(E)-(3-((triisopropylsilyl)oxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate **483**



Prepared according to general procedure **E** on a 2.2 mmol scale:

Step E1 was performed with CuCl (12.0 mg, 0.113 mmol), XantPhos (70.0 mg, 0.113 mmol) and KO^{t}Bu (40.4 mg, 0.360 mmol) in THF (6.4 mL), B_2Pin_2 (1.12 g, 4.13 mmol) in THF (3.2 mL), *(but-3-yn-2-yloxy)triisopropylsilane* **483a** (500 mg, 2.20 mmol), and methanol (250 µL, 11.6 mmol) to furnish the

intermediate pinicolatoboronic ester *(E)-triisopropyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-yl)oxy)silane* as a yellow oil for direct consumption in step E2.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.61 (dd, $\mathcal{J}$ = 18.0, 4.6 Hz, 1H, H-2), 5.62 (dd, $\mathcal{J}$ = 18.0, 1.5 Hz, 1H, H-1), 4.47–4.39 (m, 1H, H-3). H-4,11,12 were obscured by pinacol methyl groups.

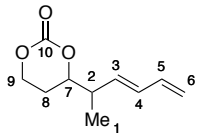
Step E2 was performed with ammonium acetate (1.12 g, 14.5 mmol) and sodium *meta*-periodate (3.07 g, 14.5 mmol) in acetone (15 mL) and water (15 mL) to furnish a crude yellow oil containing the intermediate boronic acid *(E)-(3-((triisopropylsilyl)oxy)but-1-en-1-yl)boronic acid* for immediate use in step E3.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.50 (dd, $\mathcal{J}$ = 17.9, 4.7 Hz, 1H, H-2), 5.59 (dd, $\mathcal{J}$ = 17.9, 1.4 Hz, 1H, H-1), 4.47–4.38 (m, 1H, H-3). H-4,11,12 were obscured by impurities.

Step E3 was performed in dichloromethane (18 mL) with boron trifluoride diethyl etherate (320 µL, 2.60 mmol) and mesityl iodonium diacetate (1.05 g, 2.60 mmol) in a solution of dichloromethane (9 mL). The reaction was quenched with the addition of potassium trifluoromethanesulfonate (880 mg, 4.40 mmol) and water (50 mL) and purified by silica column chromatography, eluting with 0–20% acetone in dichloromethane. The resulting purified iodonium salt was precipitated with hexanes to furnish the title compound as an amorphous off-white solid (421 mg, 0.68 mmol, 31% over three steps).

IR ν_{max}/cm^{-1} (film): 2945, 2893, 2867, 1592 (C=C), 1463, 1405, 1382, 1276, 1237, 1224, 1159, 1099, 1026; ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 7.09 (s, 2H, H-7), 6.72 (dd, $\mathcal{J}$ = 13.9, 1.2 Hz, 1H, H-1), 6.29 (dd, $\mathcal{J}$ = 13.9, 5.0 Hz, 1H, H-2), 4.54 (app. qn, $\mathcal{J}$ = 5.7 Hz, 1H, H-3), 2.57 (s, 6H, H-9), 2.35 (s, 3H, H-10), 1.24 (d, $\mathcal{J}$ = 6.4 Hz, 3H, H-4), 0.97–0.90 (m, 21H, H-11,12); ^{13}C NMR (100 MHz, CDCl3) δ (ppm): 150.2 (C-2), 144.5 (C-8), 142.8 (C-6), 130.3 (C-7), 120.3 (q, $^1\mathcal{J}$ = 313.3 Hz, C-Tf), 117.0 (C-5), 97.8 (C-1), 70.6 (C-3), 27.0 (C-9), 23.9 (C-10), 21.2 (C-4), 18.0 (C-12), 17.9 (C-12'), 12.2 (C-11); ^{19}F NMR (376 MHz, $CDCl_3$) *δ*: −79.3; HRMS-ESI (*m/z*) found $[M–OTf]^+$ 473.1720, $C_{22}H_{38}OSiI$ requires 473.1731.

(E)-4-(hexa-3,5-dien-2-yl)-1,3-dioxan-2-one **484**

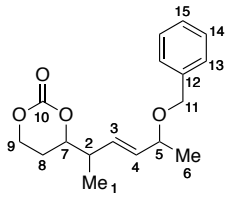


Prepared according to a procedure adapted from Gaunt et al.[158] To a solution of *(E)-pent-3-en-1-yl dimethylcarbamate* **317** (31.6 mg, 200 µmol) and $(CuOTf)_2$•PhH (5.2 mg, 10 µmol) in dichloromethane (2 mL) was added *(E)-(3-(benzyloxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate* **481** (222 mg, 400 µmol) in dichloromethane (2 mL), with the resulting mixture stirred at room temperature for 24 hours. The reaction was quenched by the addition of triethylamine (0.5 mL) and sat aq. $NaHCO_3$ (5 mL) and was vigorously stirred for five minutes. The phases were separated and the aqueous phase extracted with

further portions of dichloromethane (2 x 5 mL). The organic fractions were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified twice with silica column chromatography, eluting firstly with 20% ethyl acetate in petroleum ether 40–60 and secondly in a gradient of 0–2% diethyl ether in dichloromethane, to furnish the title compound as an inseparable 3:1 mixture of diasteroisomers (2.0 mg, 11 μmol, 5%).

R_F 0.28 (2% Et_2O in CH_2Cl_2); IR ν_{max}/cm^{-1} (film): 2970, 2926, 2853, 1744 (C=O), 1605, 1481, 1457, 1408, 1250, 1221, 1195; *Major diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.37–6.24 (m, 1H, H-5 [obscured]), 6.20–6.10 (m, 1H, H-4 [obscured]), 5.57 (dd, J = 15.2, 8.2 Hz, 1H, H-3), 5.22–5.15 (m, 1H, H-6a [obscured]), 5.10–5.06 (m, 1H, H-6b [obscured]), 4.46–4.30 (m, 2H, H-9 [obscured]), 4.26 (ddd, J = 10.7, 7.2, 3.5, 1H, H-7), 2.53 (app. sx, J = 7.0 Hz, 1H, H-2 [obscured]), 2.07–1.87 (m, 2H, H-8 [obscured]), 1.18 (d, J = 6.6 Hz, 1H, H-1 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.1 (C-10), 136.5 (C-5), 133.3 (C-4), 133.0 (C-3), 117.5 (C-6), 82.5 (C-7), 67.0 (C-9), 41.7 (C-2), 25.1 (C-8), 15.8 (C-1); *Minor diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.37–6.24 (m, 1H, H-5 [obscured]), 6.20–6.10 (m, 1H, H-4 [obscured]), 5.65 (dd, J = 15.3, 8.2 Hz, 1H, H-3), 5.22–5.15 (m, 1H, H-6a [obscured]), 5.10–5.06 (m, 1H, H-6b [obscured]), 4.46–4.30 (m, 3H, H-7,9 [obscured]), 2.53 (m, 1H, H-2 [obscured]), 2.07–1.87 (m, 2H, H-8 [obscured]), 1.17 (d, J = 6.5 Hz, 1H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.2 (C-10), 136.6 (C-5), 133.4 (C-4), 132.8 (C-3), 117.3 (C-6), 82.5 (C-7), 67.0 (C-9), 41.1 (C-2), 24.5 (C-8), 15.5 (C-1); HRMS-ESI (*m/z*) found M^+ 183.1015, $C_{10}H_{15}O_3$ requires 183.1016.

(E)-4-(5-(benzyloxy)hex-3-en-2-yl)-1,3-dioxan-2-one **478**

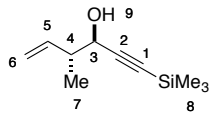


A solution of *(E)-(3-(benzyloxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate* **481** (222 mg, 400 μmol) in dichloromethane (2 mL) was added at 0 °C to a solution of *(E)-pent-3-en-1-yl dimethylcarbamate* **317** (31.6 mg, 200 μmol) and $(CuOTf)_2$•PhH (5.2 mg, 10 μmol) in dichloromethane (2 mL). The resulting mixture was stirred at 0 °C for 24 hours before quenching by the addition of triethylamine (0.5 mL) and sat. aq. $NaHCO_3$ (5 mL) and vigorously stirring the reaction mixture for five minutes. The phases were separated and the aqueous phase was extracted with further portions of dichloromethane (2 x 5 mL). The organic fractions were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica column chromatography, eluting with 20% ethyl acetate in petroleum ether 40–60 to furnish the title compound as an inseparable mixture of four diastereoisomers (11.6 mg, 40 μmol, 20%).

R_F 0.11 (40% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2976, 2930, 1749 (C=O), 1454, 1407, 1250, 1194, 1116, 1071, 1028; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.27 (m, 5H, H-13,14,15), 5.66–5.51 (m, 2H, H-3,4), 4.56–4.51 (m, 1H, H-11a), 4.67–4.25 (m, 4H, H-7,9,11b), 3.94 (app. sx, $\mathcal{J}$ = 6.3 Hz, 1H, H-5), 2.57–2.48 (m, 1H, H-2), 2.05–1.87 (m, 2H, H-8), 1.31–1.28 (m, 3H, H-6), 1.20–1.14 (m, 3H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.2 (C-10), 138.9 (C-12), 135.2 (C-3), 131.3 (C-4), 131.1 (C-4'), 128.6 (C-14), 127.8 (2C, C-13,15), 82.6 (C-7), 82.5 (C-7'), 75.82 (C-5), 75.78 (C-5'), 75.7 (C-5''), 75.6 (C-5'''), 70.5 (C-11), 70.3 (C-11'), 67.1 (C-9), 41.4 (C-2), 41.3 (C-2'), 40.9 (C-2''), 25.1 (C-8), 24.8 (C-8'), 21.8 (C-6), 16.0 (C-1), 15.7 (C-1'); HRMS-ESI (*m/z*) found $[M+H]^+$ 291.1588, $C_{17}H_{23}O_4$ requires 291.1591.

6.3.3. First generation synthetic approach

(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol **511**[221]



Method 1:

Adapted from a procedure reported by Curran et al.[192] Freshly condensed *trans*-butene (approx. 3.0 mL, 34 mmol) was added *via* canula to a −78 °C stirred solution of potassium *tert*-butoxide (510 mg, 4.30 mmol) in tetrahydrofuran (28 mL). *n*-BuLi (1.6 M in hexanes, 2.70 mL, 4.30 mmol) was then added to the reaction with the resulting vivid yellow solution then warmed to −45 °C and maintained at this temperature for 30 minutes. The mixture was cooled to −78 °C and a solution of (+)–methoxydi*iso*pinocampheylborane (1.36 g, 4.30 mmol) in tetrahydrofuran (7 mL) added. The resulting suspension was then stirred for a further 40 minutes before undergoing a dropwise addition of boron trifluoride diethyl etherate (540 µL, 4.30 mmol) over a 30-minute period. 3-trimethylsilylpropynal (313 µL, 2.14 mmol) was introduced to the crotylation mixture and the resulting solution was stirred for 6 hours at −78 °C. The reaction mixture was quenched by the dropwise addition of methanol (1.4 mL) and warmed to room temperature. The product mixture was concentrated *in vacuo* and the residue dissolved in 2:1 mixture of THF/H_2O (21 mL), cooled to 0 °C. Sodium perborate tetrahydrate (2.15 g, 14.0 mmol) was added portionwise and the suspension stirred for 14 hours. The resulting mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residues were purified by silica column chromatography, eluting with 5% ethyl acetate in petroleum ether 40–60 to furnish the title compound as a colourless oil (100 mg, 0.55 mmol, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.80 (ddd, $\mathcal{J}$ = 17.1, 10.5, 7.6 Hz, 1H, H-5), 5.18–5.12 (m, 2H, H-6), 4.18 (app. t, $\mathcal{J}$ = 5.9 Hz, 1H, H-3), 2.44 (app. sx, $\mathcal{J}$ = 6.9 Hz, 1H, H-4), 1.97 (d, $\mathcal{J}$ = 5.7 Hz, 1H, H-9), 1.12 (d, $\mathcal{J}$ = 7.1 Hz, 3H, H-7), 0.17 (s, 9H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3 (C-

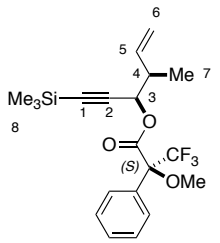
5), 116.6 (C-6), 105.2 (C-2), 90.5 (C-1), 66.6 (C-3), 44.4 (C-4), 15.3 (C-7), −0.1 (C-8); $[\alpha]^{25}_{D}$ = +26.3 ° (c = 1.0, $CHCl_3$), literature (enant-X): $[\alpha]^{27}_{D}$ = −30 ° (c = 1.1, $CHCl_3$); GC-FID analysis (Chiraldex β-DM column, 70 °C to 130 °C at a rate of 6 °C min^{-1} then hold for 5 minutes, linear velocity = 50 cm s^{-1}, split ratio = 50.0) indicated 93% *e.e.*: t_R (major) = 6.82 minutes, t_R (minor) = 7.02 minutes. Experimental data in agreement with previous literature report.[221]

Method 2:

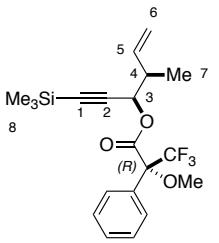
Adapted from a procedure reported by Roush et al.[193] An oven-dried flask was charged with powdered 4 Å molecular sieves (14.4 g, previously dried by heating *in vacuo* for 18 hours) and backfilled with nitrogen gas. Anhydrous toluene (192 mL) and a solution of (*S,S*)-diisopropyl tartrate (*E*)-crotylboronate in toluene (82 mL, 0.72 M, 59.0 mmol – freshly prepared according to the procedure reported by Roush *et al.)*[193] were added *via* syringe. This suspension was stirred at room temperature for a period of 30 minutes before being cooled to −78 °C and undergoing a dropwise addition of a solution of freshly-distilled 3-trimethylsilylpropynal (6.16 g, 48.7 mmol) in anhydrous toluene (18 mL) over one hour. The reaction mixture was maintained at −78 °C for two hours before quenching by the addition of 2 M aq. NaOH (156 mL). The resulting mixture was gradually warmed to room temperature over one hour and was vigorously stirred for a further 30 minutes. The quenched biphasic reaction mixture was separated and the aqueous layer extracted with diethyl ether (3 x 120 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ solution (100 mL) and brine (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude oily residue was purified by silica column chromatography, eluting with 5% diethyl ether in petroleum ether 40–60, to give the title compound as a colourless oil (7.61 g, 41.7 mmol, 86%).

$[\alpha]^{26}_{D}$ = +23.7 ° (c = 1.0, $CHCl_3$), literature (enant-**511**): $[\alpha]^{27}_{D}$ = −30 ° (c = 1.1, $CHCl_3$); GC-FID analysis (Chiraldex β-DM column, 70 °C to 130 °C at a rate of 6 °C min^{-1} then hold for 5 minutes, linear velocity = 50 cm s^{-1}, split ratio = 50.0) indicated 75% *e.e.*: t_R (major) = 6.86 minutes, t_R (minor) = 7.06 minutes. Spectroscopic data identical with those described in method 1.

Mosher ester analysis was carried out to confirm enantiomer according to the method described by Shao et al.[222]



511a



511b

R-(−)-MTPA-Cl (36 µL, 0.19 mmol) was added to a solution of *(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol* **511** (18.2 mg, 0.100 mmol) and dry pyridine (23 µL, 0.30 mmol) in dichloromethane (1.5 mL) and the resulting mixture was stirred for 24 hours. The reaction was quenched with the addition of sat.

aq. $NaHCO_3$ solution (1.5 mL), the phases separated, and the aqueous phase extracted with diethyl ether (2 x 2 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under a stream of nitrogen gas. The resulting residues were purified by silica column chromatography, eluting in a gradient of 0–2% diethyl ether in petroleum ether 40–60, to furnish the *S*-MTPA ester **511a** as a colourless oil (6.7:1 *d.r.*).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59–7.50 (m, 2H, H-Ar), 7.42–7.35 (m, 3H, H-Ar), 5.74 (ddd, $\mathcal{J}$ = 17.5, 10.2, 7.6 Hz, 1H, H-5), 5.41 (d, $\mathcal{J}$ = 6.9 Hz, 1H, H-3), 5.17–5.08 (m, 2H, H-6), 3.54 (s, 3H, H-OMe), 2.63 (app. sx, $\mathcal{J}$ = 7.0 Hz, 1H, H-4), 1.15 (d, $\mathcal{J}$ = 6.8 Hz, 3H, H-7), 0.15 (s, 9H, H-8).

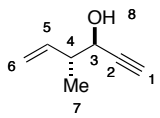
R-MTPA ester **511b** (6.7:1 *d.r.*) was prepared in an identical fashion with *S*-(−)-MTPA-Cl.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59–7.50 (m, 2H, H-Ar), 7.42–7.35 (m, 3H, H-Ar), 5.68 (ddd, $\mathcal{J}$ = 17.2, 10.3, 7.6 Hz, 1H, H-5), 5.46 (d, $\mathcal{J}$ = 6.2 Hz, 1H, H-3), 5.08–5.01 (m, 2H, H-6), 3.59 (s, 3H, H-OMe), 2.57 (app. sx, $\mathcal{J}$ = 6.8 Hz, 1H, H-4), 1.09 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7), 0.18 (s, 9H, H-8). Comparitive analysis shown below (Table 44).

Proton	**δ *S*-ester (511a) (ppm)**	**δ *R*-ester (511a) (ppm)**	**$\Delta\delta^{SR}$ ($\delta_S - \delta_R$)**	
			ppm	**Hz (400 MHz)**
3	5.41	5.46	−0.05	−20
8	0.15	0.18	−0.03	−12
4	2.63	2.57	+0.06	+24
5	5.74	5.68	+0.06	+24
7	1.15	1.09	+0.06	+24

Table 44 – Mosher ester analysis of crotylation product **511**

(3R,4R)-4-methylhex-5-en-1-yn-3-ol **514**

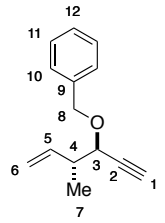


Potassium carbonate (56.0 g, 405 mmol) was added portionwise to a solution of *(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol* **511** (7.73 g, 96% purity, 40.7 mmol) in methanol (200 mL). The resulting cloudy suspension was stirred for 15 minutes then filtered through a pad of celite™ and the filter cake

washed with diethyl ether (2 x 200 mL) and water (100 mL). The resulting biphasic mixture was separated and the aqueous layer extracted with further portions of diethyl ether (2 x 100 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by kugelrohr distillation to furnish the title compound as a colourless oil (3.22 g, 29.2 mmol, 72%).

IR ν_{max}/cm^{-1} (film): 3385 (br., O–H), 3298 (*sp* C–H), 2972, 2876, 1641 (C=C), 1457, 1417, 1374, 1288, 1027, 997, 918; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.82 (ddd, $\mathcal{J}$ = 17.1, 10.5, 7.5 Hz, 1H, H-5), 5.21–5.14 (m, 2H, H-6), 4.22 (d, $\mathcal{J}$ = 5.1 Hz, 1H, H-3), 2.53–2.42 (m, 2H, H-1,4), 2.02 (br. s, 1H, H-8), 1.14 (d, $\mathcal{J}$ = 6.8 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.0 (C-5), 117.1 (C-6), 83.3 (C-2), 74.0 (C-1), 66.1 (C-3), 44.3 (C-4), 15.2 (C-7); HRMS-ESI (*m/z*) found M^+ 110.0733, $C_7H_{10}O$ requires 110.0732; $[\alpha]_D^{26}$ = +31.3 ° (c = 1.0, $CHCl_3$).

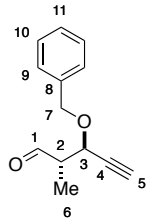
((((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)methyl)benzene **517**



Adapted from a procedure reported by Nakai et al.[197] Benzyl bromide (2.32 mL, 19.5 mmol) was added dropwise at 0 °C to a vigorously stirred mixture of *(3R,4R)-4-methylhex-5-en-1-yn-3-ol* **514** (1.65 g, 15.0 mmol), tetrabutylammonium iodide (276 mg, 0.75 mmol), NaOH (2.4 g, 60.0 mmol) and water (0.75 mL). The resulting reaction mixture was warmed to room temperature and stirred for 16 hours before being diluted with diethyl ether (20 mL) and filtered. Water (20 mL) was added to the filtrate and the biphasic mixture was separated, with the aqueous layer extracted with further portions of diethyl ether (3 x 20 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by alumina column chromatography, eluting with 0 to 1% diethyl ether in petroleum ether 40–60, to give the title compound as colourless oil (2.41 g, 12.1 mmol, 81%).

R_F 0.41 (2% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3298 (*sp* C–H), 2980, 2869, 1643 (C=C), 1496, 1453, 1344, 1205, 1084, 1066, 918, 696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40–7.27 (m, 5H, H-10,11,12), 5.88 (ddd, $\mathcal{J}$ = 17.4, 10.3, 7.2 Hz, 1H, H-5), 5.16–5.07 (m, 2H, H-6), 4.84 (d, $\mathcal{J}$ = 11.9 Hz, 1H, H-8a), 4.53 (d, $\mathcal{J}$ = 11.9 Hz, 1H, H-8b), 4.01 (dd, $\mathcal{J}$ = 5.7, 2.0 Hz, 1H, H-3), 2.58 (app. sx, $\mathcal{J}$ = 6.7 Hz, 1H, H-4), 2.49 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-1), 1.17 (d, $\mathcal{J}$ = 6.7 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.7 (C-5), 138.0 (C-9), 128.5 (C-11), 128.1 (C-10), 127.8 (C-12), 115.5 (C-6), 81.4 (C-2), 75.0 (C-1), 72.6 (C-3), 70.7 (C-8), 42.4 (C-4), 15.4 (C-7); HRMS-ESI (*m/z*) found $[M+NH_4]^+$ 218.1541, $C_{14}H_{20}ON$ requires 218.1539; $[\alpha]_D^{26}$ = +83.9 ° (c = 1.0, $CHCl_3$).

(2S,3R)-3-(benzyloxy)-2-methylpent-4-ynal **518**



Prepared according to general procedure **F** on a 4.0 mmol scale.

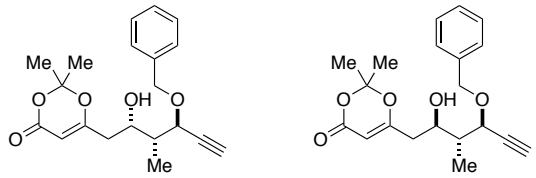
Step F1 was performed with NMO (3.33 mL, 50 wt% in water, 16.0 mmol), OsO_4 (162 µL, 2.5 wt% in *tert*-butanol, 16.0 µmol) and *((((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)methyl)benzene* **517** (800 mg, 4.00 mmol) with stirring for 168 hours. The resulting solution was quenched with sat. aq. $Na_2S_2O_3$ solution (200 mL) and ethyl acetate (200 mL). Following separation, the aqueous layer was washed with ethyl acetate (4 x 100 mL) to furnish the crude diol mixture as 2:1 mixture of diastereoisomers.

Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42–7.30 (m, 5H, H-9,10,11), 4.90 (d, J = 11.4 Hz, 1H, H-7a [obscured]), 4.56 (d, J = 11.4 Hz, 1H, H-7b), 4.28 (dd, J = 7.0, 2.1 Hz, 1H, H-3), 3.75 (dd, J = 11.0, 3.0 Hz, 1H, H-0a), 3.71–3.65 (m, 1H, H-1), 3.60–3.56 (m, 1H, H-0b [obscured]), 2.76 (br. s, 2H, O–H), 2.58 (d, J = 2.1 Hz, 1H, H-5), 2.11 (app. sx, J = 7.1 Hz, 1H, H-2), 1.05 (d, J = 6.8 Hz, 3H, H-6). *Minor diastereoisomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42–7.30 (m, 5H, H-9,10,11), 4.88 (d, J = 11.6 Hz, 1H, H-7a [obscured]), 4.51 (d, J = 11.6 Hz, 1H, H-7b), 4.19–4.11 (m, 2H, H-1,3), 3.81 (br. t, J = 4.6 Hz, 1H, O–H), 3.66–3.55 (m, 2H, H-0 [obscured], 2.59 (d, J = 2.1 Hz, 1H, H-5), 2.42 (br. s, 1H, O–H), 2.05–1.96 (m, 1H, H-3), 1.08 (d, J = 7.1 Hz, 3H, H-6).

Step F2 was performed with silica-supported sodium *meta*-periodate (40.0 g, approx. 15 wt% $NaIO_4$, 28.0 mmol) in dichloromethane (400 mL). The crude residue was purified by silica column chromatography, eluting with 2–3% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (647 mg, >98% diasteromeric purity, 3.20 mmol, 80%).

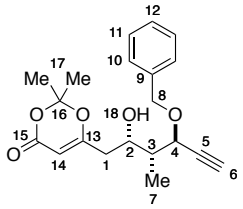
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.76 (d, J = 1.7 Hz, 1H, H-1), 7.39–7.27 (m, 5H, H-9,10,11), 4.84 (d, J = 11.7 Hz, 1H, H-7a), 4.53 (d, J = 11.7 Hz, 1H, H-7b), 4.34 (dd, J = 6.8, 2.1 Hz, 1H, H-3), 2.72 (app. qd, J = 6.0, 1.8 Hz, 1H, H-2), 2.59 (d, J = 2.1 Hz, 1H, H-5), 1.20 (d, J = 7.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 202.3 (C-1), 137.2 (C-8), 128.6 (C-10), 128.2 (C-9), 128.1 (C-11), 80.2 (C-4), 76.4 (C-5), 71.0 (C-7), 68.9 (C-3), 50.8 (C-2), 10.6 (C-6). Consumed directly.

6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **520** and 6-*((2R,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **epi-520**



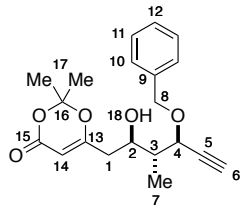
Prepared according to general procedure **G** with *((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane* **459** (2.94 g, 13.7 mmol) in dichloromethane (20 mL), boron trifluoride diethyl etherate (0.56 mL, 4.5 mmol) in dichloromethane (20 mL) and *(2S,3R)-3-(benzyloxy)-2-methylpent-4-ynal* **518** (672 mg, 95% purity, 3.33 mmol) in dichloromethane (40 mL). The reaction mixture was quenched with triethylamine (5 mL) and sat. aq. $NaHCO_3$ solution (20 mL) and the work-up performed with dichloromethane (2 x 50 mL) and brine (40 mL). The crude residue was purified by silica column chromatography, eluting with 10–50% ethyl acetate in petroleum ether 40–60 to give the title compounds in a 5:1 ratio. The mixture of diastereoisomers was further purified by silica column chromatography, eluting with 10% diethyl ether in toluene, to furnish the title compound **520** (872 mg, 2.53 mmol, 76%) and its C-2 epimer **epi-520** (152 mg, 0.44 mmol, 13%) as white crystalline solids.

6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **520**



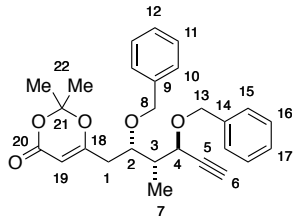
R_F 0.20 (40% EtOAc in pet. ether 40–60); T_m 78–80 °C; IR ν_{max}/cm^{-1} (film): 3464 (br., O–H), 3290 (*sp* C–H), 2980, 1717 (C=O), 1633 (C=C), 1457, 1391, 1376, 1274, 1203, 1017; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.30 (m, 5H, H-10,11,12), 5.31 (s, 1H, H-14), 4.86 (d, J = 11.7 Hz, 1H, H-8a), 4.49 (d, J = 11.7 Hz, 1H, H-8b), 4.43 (dddd, J = 8.8, 5.0, 3.6, 1.8 Hz, 1H, H-2), 4.11 (dd, J = 5.4, 2.1 Hz, 1H, H-4), 2.72 (d, J = 3.6 Hz, 1H, H-18), 2.58 (d, J = 2.1 Hz, 1H, H-6), 2.36 (dd, J = 14.6, 8.8 Hz, 1H, H-1a), 2.24 (dd, J = 14.6, 5.0 Hz, 1H, H-1b), 1.91 (qdd, J = 7.1, 5.4, 1.8 Hz, 1H, H-3), 1.683 (s, 3H, H-17a), 1.677 (s, 3H, H-17b), 1.05 (d, J = 7.1 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.4 (C-13), 161.3 (C-15), 136.9 (C-9), 128.8 (C-11), 128.4 (2C, C-10,12), 106.7 (C-16), 95.1 (C-14), 81.3 (C-5), 76.0 (C-6), 72.4 (C-4), 71.3 (C-8), 68.5 (C-2), 42.4 (C-3), 38.7 (C-1), 25.5 (C-17a), 24.9 (C-17b), 10.5 (C-7); HRMS-ESI (*m/z*) found $[M+H]^+$ 345.1698, $C_{20}H_{25}O_5$ requires 345.1697; $[\alpha]^{25}_D$ = +43.1° (c = 1.0, $CHCl_3$).

6-((2R,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **epi-520**



R_F 0.15 (40% EtOAc in pet. ether 40–60); T_m 69–72 °C; IR ν_{max}/cm^{-1} (film): 3440 (br., O–H), 3286 (*sp* C–H), 2929, 1709 (C=O), 1631 (C=C), 1455, 1391, 1378, 1276, 1203, 1013; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.29 (m, 5H, H-10,11,12), 5.33 (s, 1H, H-14), 4.86 (d, $\mathcal{J}$ = 11.7 Hz, 1H, H-8a), 4.51 (d, $\mathcal{J}$ = 11.7 Hz, 1H, H-8b), 4.20 (dd, $\mathcal{J}$ = 6.9, 2.1 Hz, 1H, H-4), 3.93–3.87 (m, 1H, H-2), 2.92 (d, $\mathcal{J}$ = 4.1 Hz, 1H, H-18), 2.57 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-6), 2.50 (dd, $\mathcal{J}$ = 14.7, 3.1 Hz, 1H, H-1a), 2.30 (dd, $\mathcal{J}$ = 14.7, 9.5 Hz, 1H, H-1b), 1.91 (app. sx, $\mathcal{J}$ = 7.0 Hz, 1H, H-3), 1.693 (s, 3H, H-17a), 1.687 (s, 3H, H-17b), 1.04 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.6 (C-13), 161.2 (C-15), 137.2 (C-9), 128.7 (C-11), 128.3 (C-10), 128.2 (C-12) 106.7 (C-16), 95.5 (C-14), 81.0 (C-5), 76.0 (C-6), 72.0 (C-4), 71.4 (C-2), 71.2 (C-8), 43.7 (C-3), 39.1 (C-1), 25.6 (C-17a), 24.7 (C-17b), 12.9 (C-7); HRMS-ESI (*m/z*) found $[M+H]^+$ 345.1698, $C_{20}H_{25}O_5$ requires 345.1697; $[\alpha]_D^{26}$ = +62.9 ° (c = 1.0, $CHCl_3$).

6-((2S,3R,4R)-2,4-bis(benzyloxy)-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **521**

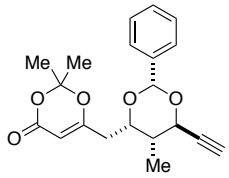


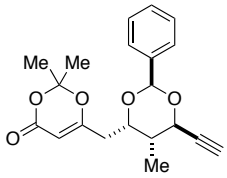
Adapted from a procedure reported by Kunishima et al.[202] Trifluoromethanesulfonic acid (1.8 µL, 20 µmol) was added to a stirred suspension of *6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **520** (34.4 mg, 100 µmol), *2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT)* **523** (13.8 mg, 40 µmol) and 5 Å molecular sieves (13.0 mg, freshly dried) in 1,4-dioxane (0.5 mL). The resulting mixture was stirred at room temperature for 22 hours before quenching on the addition of triethylamine (10 µL). The product mixture was filtered through a pad of Celite™ and the resulting filtrate concentrated under a stream of nitrogen gas. The residue was re-dissolved in ethyl acetate (1 mL), washed with sat. aq. $NaHCO_3$, and the organic layer passed through a plug of anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica column chromatography, eluting with a gradient of 0 to 10% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a colourless oil (11.0 mg, 25 µmol, 25%).

R_F 0.22 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3286 (*sp* C–H), 2924, 2857, 1730 (C=O), 1633 (C=C), 1457, 1389, 1376, 1274, 1205, 1064; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32–7.26 (m, 8H, H-11,12,15,16,17), 7.21–7.17 (m, 2H, H-10), 5.28 (s, 1H, H-19), 4.79 (d, $\mathcal{J}$ = 11.4 Hz, 1H, H-13a),

4.48 (d, $\mathcal{J}$ = 11.4 Hz, 1H, H-8a), 4.33 (d, $\mathcal{J}$ = 11.4 Hz, 1H, H-13b), 4.31 (d, $\mathcal{J}$ = 11.4 Hz, 1H, H-8b), 4.11–4.05 (m, 2H, H-2,4), 2.59 (dd, $\mathcal{J}$ = 14.3, 6.4 Hz, 1H, H-1a), 2.52 (d, $\mathcal{J}$ = 2.0 Hz, 1H, H-6), 2.39 (dd, $\mathcal{J}$ = 14.3, 7.0 Hz, 1H, H-1b), 1.97 (app. dqd, $\mathcal{J}$ = 9.0, 7.0, 2.0 Hz, 1H, H-3), 1.63 (s, 3H, H-22a), 1.60 (s, 3H, H-22b), 1.10 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.2 (C-18), 161.1 (C-20), 138.2 (C-9), 137.8 (C-14), 128.5 (2C, C-11,16), 128.3 (C-15), 128.0 (C-17), 127.9 (C-12), 127.7 (C-10), 106.7 (C-21), 95.1 (C-19), 82.0 (C-5), 75.5 (C-6), 74.9 (C-2), 72.4 (C-8), 70.7 (C-13), 70.2 (C-4), 42.2 (C-3), 36.8 (C-1), 25.6 (C-22a), 24.8 (C-22b), 10.1 (C-7); HRMS-ESI (*m/z*) found $[M+Na]^+$ 457.1972, $C_{27}H_{30}O_5Na$ requires 457.1985; $[\alpha]_D^{26}$ = +34.3 ° (c = 0.3, $CHCl_3$).

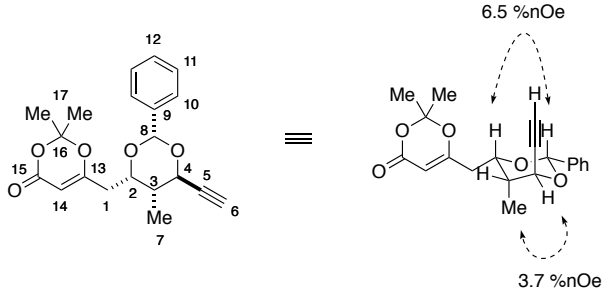
6-(((2S,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **525** and *6-(((2R,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **524**





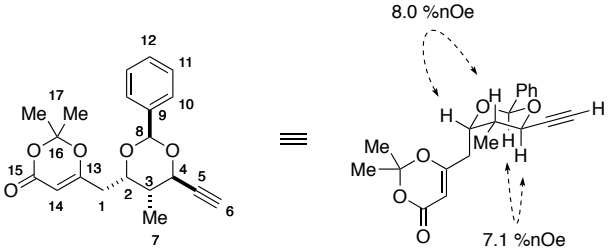
Adapted from a procedure reported by Oikawa et al.[204] DDQ (17.0 mg, 75 μmol) was added to a stirred suspension of *6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **520** (17.2 mg, 50 μmol) and 3 Å molecular sieves (20.0 mg, freshly activated) in dichloromethane (0.5 mL) contained in a microwave tube. The reaction vessel was sealed and the resulting mixture was heated to 45 °C for 24 hours before diluting with a further 2 mL dichloromethane and quenching with the addition of sat. aq $NaHCO_3$ solution (2 mL). The phases were separated and the aqueous layer extracted with a further 2 mL of dichloromethane. The combined organic fractions were passed through a plug of anhydrous $MgSO_4$ and concentrated under a stream of nitrogen gas. The resulting crude product mixture was combined with residues gathered from a second reaction (50 μmol substrate, performed analogously except for use of dichloroethane as reaction solvent and with heating to 70 °C for 24 hours). The combined mixtures were purified by silica column chromatography, eluting with 10–30% ethyl acetate in petroleum ether 40–60, to furnish the title compounds *6-(((2S,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **525** (6.4 mg, 19 μmol, 19%) and *6-(((2R,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **524** (6.5 mg, 19 μmol, 19%) both as colourless oils.

6-(((2S,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **525**



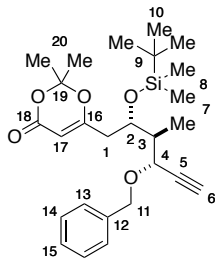
R_F 0.24 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3282 (*sp* C–H), 2920, 1722 (C=O), 1635 (C=C), 1459, 1391, 1374, 1272, 1253, 1116, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49–7.43 (m, 2H, H-11), 7.39–7.34 (m, 3H, H-10,12), 6.04 (s, 1H, H-8), 5.39 (s, 1H, H-14), 4.75 (dd, $\mathcal{J}$ = 2.2, 1.4 Hz, 1H, H-4), 4.66 (ddd, $\mathcal{J}$ = 8.8, 4.8, 2.2 Hz, 1H, H-2), 2.72 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-6), 2.59 (dd, $\mathcal{J}$ = 15.0, 8.8 Hz, 1H, H-1a), 2.32 (ddd, $\mathcal{J}$ = 15.0, 4.8, 0.5 Hz, 1H, H-1b), 1.76 (qdd, $\mathcal{J}$ = 7.0, 2.2, 1.4 Hz, 1H, H-3), 1.70 (s, 3H, H-17a), 1.68 (s, 3H, H-17b), 1.26 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.3 (C-13), 161.1 (C-15), 137.9 (C-9), 129.2 (C-12), 128.5 (C-11), 126.2 (C-10), 106.8 (C-16), 96.7 (C-8), 95.5 (C-14), 80.6 (C-5), 77.3 (C-6), 72.3 (C-2), 70.7 (C-4), 37.2 (C-1), 36.4 (C-3), 25.5 (C-17a), 24.9 (C-17b), 12.0 (C-7); HRMS-ESI (*m/z*) found $[M+Na]^+$ 365.1366, $C_{20}H_{22}O_5Na$ requires 365.1359; $[\alpha]_D^{26}$ = –23.3 ° (c = 0.15, $CHCl_3$).

6-(((2R,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **524**



R_F 0.18 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3278 (*sp* C–H), 2925, 2853, 1724 (C=O), 1635 (C=C), 1459, 1395, 1378, 1272, 1203, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46–7.42 (m, 2H, H-11), 7.38–7.31 (m, 3H, H-10,12), 5.75 (s, 1H, H-8), 5.37 (d, $\mathcal{J}$ = 0.8 Hz, 1H, H-14), 4.54–4.47 (m, 2H, H-2,4), 2.93 (dd, $\mathcal{J}$ = 14.9, 12.0 Hz, 1H, H-1a), 2.60–2.52 (m, 2H, H-3,6), 2.46 (ddd, $\mathcal{J}$ = 14.9, 3.9, 0.8 Hz, 1H, H-1b), 1.62 (s, 3H, H-17a), 1.57 (s, 3H, H-17b), 1.02 (d, $\mathcal{J}$ = 7.2 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.5 (C-13), 161.0 (C-15), 137.3 (C-9), 129.3 (C-12), 128.5 (C-11), 126.3 (C-10), 107.2 (C-16), 95.8 (C-14), 94.7 (C-8), 80.4 (C-5), 75.0 (C-6), 73.6 (C-2), 68.9 (C-4), 37.3 (C-3), 30.4 (C-1), 26.0 (C-17a), 24.3 (C-17b), 13.0 (C-7); HRMS-ESI (*m/z*) found $[M+Na]^+$ 365.1360, $C_{20}H_{22}O_5Na$ requires 365.1359; $[\alpha]_D^{26}$ = –40.0 ° (c = 0.13, $CHCl_3$).

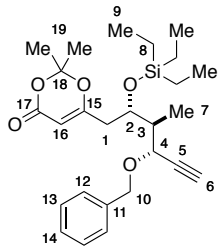
6-((2S,3S,4R)-4-(benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **526**



Tert-butyldimethylsilyl chloride (181 mg, 1.20 mmol) was added at 0 °C to a stirred suspension of *6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **520** (344 mg, 1.00 mmol) and imidazole (102 mg, 1.50 mmol) in dichloromethane (5 mL). The resulting mixture was warmed to room temperature and stirred for 24 hours, then refluxed for a further 18 hours. The reaction mixture was cooled to room temperature, diluted with dichloromethane (20 mL), and quenched with sat. aq. $NaHCO_3$ solution (25 mL). The phases were separated and the aqueous layer was extracted with further portions of dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude reaction mixture (predominantly starting material) was purified by silica column chromatography, eluting with 0–30% ethyl acetate in petroleum ether 40–60, to furnish recovered starting material (305 mg, 0.91 mmol, 91%) as a white solid and the title compound as a colourless oil (40 mg, 87 μmol, 9%).

R_F 0.37 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3290 (*sp* C–H), 2926, 2853, 1728 (C=O), 1633 (C=C), 1461, 1389, 1376, 1270, 1203, 1015, 834; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.26 (m, 5H, H-13,14,15), 5.24 (s, 1H, H-17), 4.84 (d, $\mathcal{J}$ = 11.2, 1H, H-11a), 4.40 (d, $\mathcal{J}$ = 11.2 Hz, 1H, H-11b), 4.36 (ddd, 7.5, 6.1, 2.1 Hz, 1H, H-2), 4.08 (dd, $\mathcal{J}$ = 8.3, 2.0 Hz, 1H, H-4), 2.53 (d, $\mathcal{J}$ = 2.0 Hz, 1H, H-6), 2.47–2.35 (m, 2H, H-1), 1.90 (qdd, $\mathcal{J}$ = 8.3, 6.9, 2.1 Hz, 1H, H-3), 1.62 (s, 3H, H-20a), 1.56 (s, 3H, H-20b), 1.06 (d, $\mathcal{J}$ = 6.9 Hz, 3H, H-7), 0.85 (s, 9H, H-10), 0.04 (s, 3H, H8a), –0.01 (s, 3H, H-8b); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.8 (C-16), 161.2 (C-18), 138.0 (C-12), 128.4 (C-14), 127.9 (C-13), 127.8 (C-15), 106.7 (C-19), 95.3 (C-17), 82.0 (C-5), 75.8 (C-6), 70.5 (C-11), 70.2 (C-4), 67.9 (C-2), 42.9 (C-3), 39.8 (C-1), 26.0 (C-20a), 25.9 (C-10), 24.3 (C-20b), 18.1 (C-9), 9.8 (C-7), –4.3 (C-8a), –4.7 (C-8b); HRMS-ESI (*m/z*) found $[M+Na]^+$ 481.2370, $C_{26}H_{38}O_5SiNa$ requires 481.2381; $[\alpha]_D^{26}$ = +12.3 ° (c = 1.0, $CHCl_3$).

6-((2S,3S,4R)-4-(benzyloxy)-3-methyl-2-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **527**

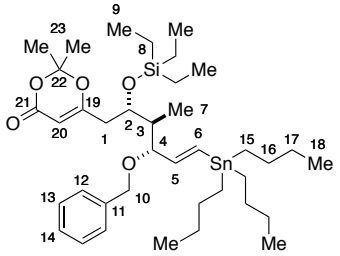


Adapted from a procedure reported by Hiemstra et al.[223] Triethylsilyl chloride (0.38 mL, 2.76 mmol) was added at 0 °C to a stirred solution of imidazole (250 mg, 3.68 mmol) and *6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **520** (250 mg, 0.74 mmol) in dimethylformamide (2.5 mL). The resulting mixture was warmed to room temperature and stirred for one hour before it was diluted with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) and sat. aq. $NaHCO_3$ solution (5 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product residue was subjected to prolonged high vacuum (approx. 0.5 mbar, 24 hours) to remove residual silanol impurities then purified by silica column chromatography, eluting with 10–20% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (287 mg, 0.63 mmol, 85%).

R_F 0.65 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3294 (*sp* C–H), 2956, 2877, 1732 (C=O), 1635 (C=C), 1459, 1389, 1372, 1272, 1203, 1066, 1013; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38–7.27 (m, 5H, H-12,13,14), 5.24 (s, 1H, H-16), 4.84 (d, $\mathcal{J}$ = 11.2, 1H, H-10a), 4.41 (d, $\mathcal{J}$ = 11.2 Hz, 1H, H-10b), 4.34 (ddd, $\mathcal{J}$ = 7.5, 6.1, 2.1 Hz, 1H, H-2), 4.08 (dd, $\mathcal{J}$ = 8.3, 2.1 Hz, 1H, H-4), 2.53 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-6), 2.48–2.35 (m, 2H, H-1), 1.88 (dqd, $\mathcal{J}$ = 8.3, 6.9, 2.1 Hz, 1H, H-3), 1.61 (s, 3H, H-19a), 1.56 (s, 3H, H-19b), 1.05 (d, $\mathcal{J}$ = 6.9 Hz, 3H, H-7), 0.92 (t, $\mathcal{J}$ = 8.2, 9H, H-9), 0.54 (q, $\mathcal{J}$ = 8.2 Hz, 6H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.9 (C-15), 161.2 (C-17), 138.0 (C-11), 128.4 (C-13), 128.1 (C-12), 127.8 (C-14), 106.7 (C-18), 95.2 (C-16), 82.0 (C-5), 75.8 (C-6), 70.6 (C-10), 70.3 (C-4), 68.0 (C-2), 43.0 (C-3), 39.9 (C-1), 26.0 (C-19a), 24.3 (C-19b), 9.7 (C-7), 7.0 (C-9), 5.2 (C-8); HRMS-ESI (*m/z*) found $[M+H]^+$ 459.2555, $C_{26}H_{39}O_5Si$ requires 459.2561; $[\alpha]_D^{26}$ = +10.7 ° (c = 1.0, $CHCl_3$).

6.3.4. Second generation approach

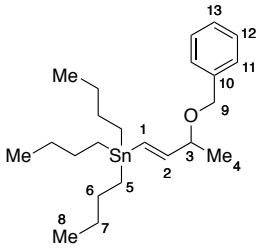
6-((2S,3S,4R,E)-4-(benzyloxy)-3-methyl-6-(tributylstannyl)-2-((triethylsilyl)oxy)hex-5-en-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **534**



Prepared according to general procedure **H** with Pd_2dba_3 (2.3 mg, 2.5 μmol) and tricylohexylphosphonium tetrafluoroborate (3.7 mg, 10 μmol) in dichloromethane (4 mL), di-*iso*-proylethylamine (3.5 μL, 10 μmol), *6-((2S,3S,4R)-4-(benzyloxy)-3-methyl-2-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **527** (163 mg, 0.50 mmol) in dichloromethane (1 mL), and tributyltin hydride (162 μL, 0.60 mmol) in dichloromethane (2 mL). Purification was carried out by silica column chromatography, eluting with 0–10% diethyl ether in petroleum ether 40–60, to furnish the title compound as a pale yellow oil (267 mg, 0.36 mmol, 72%).

R_F 0.59 (40% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2960, 2924, 2873, 1736 (C=O), 1637 (C=C), 1457, 1389, 1376, 1269, 1203, 1066, 1015; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.34–7.26 (m, 5H, H-12,13,14), 6.15 ([d+d]d, [$^2\mathcal{J}_{H-^{119}Sn}$ = 73.9 Hz], [$^2\mathcal{J}_{H-^{117}Sn}$ = 71.5 Hz], $\mathcal{J}$ = 19.0 Hz, 1H, H-6), 5.71 ([d+d]dd, [$^3\mathcal{J}_{H-^{119}Sn}$ = 61.7 Hz], [$^3\mathcal{J}_{H-^{117}Sn}$ = 59.6 Hz], $\mathcal{J}$ = 19.0, 8.1 Hz, 1H, H-5), 5.23 (s, 1H, H-20), 4.58–4.50 (m, 2H, H-2,10a), 4.22 (d, $\mathcal{J}$ = 11.4 Hz, 1H, H-10a), 4.41 (app. d, $\mathcal{J}$ = 8.6 Hz, 1H, H-4), 2.47–2.38 (m, 2H, H-1), 1.63–1.45 (m, 13H, H-3,16,23), 1.32 (app. sx, $\mathcal{J}$ = 7.3 Hz, 6H, H-17), 0.98–0.84 (m, 24H, H-9,15,18), 0.79 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7), 0.58 (q, $\mathcal{J}$ = 7.6 Hz, 6H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.3 (C-19), 161.4 (C-21), 148.0 (C-5), 139.2 (C-11), 134.1 (C-6), 128.3 (C-13), 127.7 (C-12), 127.4 (C-14), 106.7 (C-22), 95.0 (C-20), 85.8 ([d], [$^3\mathcal{J}_{C-[Sn]}$ = 60.9 Hz], C-4), 70.0 (C-10), 67.8 (C-2), 41.8 (C-3), 40.6 (C-1), 29.3 ([d], [$^3\mathcal{J}_{C-[Sn]}$ = 20.7 Hz], C-17), 27.4 ([d+d], [$^2\mathcal{J}_{C-^{119}Sn}$ = 53.9 Hz], [$^2\mathcal{J}_{C-^{117}Sn}$ = 52.2 Hz], C-16), 26.1 (C-23a), 24.2 (C-23b), 13.9 (C-18), 9.7 ([d+d], [$^1\mathcal{J}_{C-^{119}Sn}$ = 343.7 Hz], [$^1\mathcal{J}_{C-^{117}Sn}$ = 328.8 Hz], C-15), 9.2 (C-7), 7.1 (C-9), 5.3 (C-8); HRMS-ESI (*m/z*) found $[M+Na]^+$ 773.3586, $C_{38}H_{66}O_5Si^{120}SnNa$ requires 773.3601; $[\alpha]_D^{26}$ = +4.8 ° (c = 1.0, $CHCl_3$).

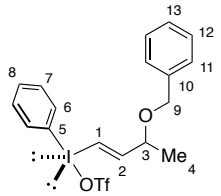
(E)-(3-(benzyloxy)but-1-en-1-yl)tributylstannane **540**



Prepared according to general procedure **H** with Pd_2dba_3 (4.6 mg, 5.0 μmol) and tricylohexylphosphonium tetrafluoroborate (7.4 mg, 20 μmol) in toluene (8 mL), di-*iso*-proylethylamine (7.0 μL, 20 μmol), *((but-3-yn-2-yloxy)methyl)benzene* **539** (160 mg, 1.00 mmol) in toluene (2 mL), and tributyltin hydride (323 μL, 1.20 mmol) in toluene (3 mL). Purification was carried out by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (187 mg, 0.41 mmol, 41%).

R_F 0.31 (2% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2956, 2925, 2871, 2853, 1600, 1455, 1389, 1135, 1098, 1070; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.31 (m, 4H, H-11,12), 7.30–7.26 (m, 1H, H-13), 6.12 ([d]d, $[^2\mathcal{J}_{H-[Sn]} = 73.5$ Hz], $\mathcal{J} = 19.1$ Hz, 1H, H-1), 5.91 ([d+d]dd, $[^3\mathcal{J}_{^{119}Sn-H} = 63.4$ Hz], $[^3\mathcal{J}_{^{117}Sn-H} = 60.6$ Hz], $\mathcal{J} = 19.1$, 7.0 Hz, 1H, H-2), 4.58 (d, $\mathcal{J} = 11.9$ Hz, 1H, H-9a), 4.38 (d, $\mathcal{J} = 11.9$ Hz, 1H, H-9b), 3.87 (app. q, $\mathcal{J} = 6.5$ Hz, 1H, H-3), 1.62–1.44 (m, 6H, H-7), 1.38–1.27 (m, 9H, H-6,4), 0.95–0.87 (m, 15H, H-8,5); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.3 (C-2), 139.1 (C-10), 130.3 ([d+d], $[^1\mathcal{J}_{C-^{119}Sn} = 367.8$ Hz], $[^1\mathcal{J}_{C-^{117}Sn} = 353.8$ Hz], C-1), 128.5 (C-12), 127.9 (C-11), 127.5 (C-13), 79.3 ([d+d], $[^3\mathcal{J}_{C-^{119}Sn} = 64.7$ Hz], $[^3\mathcal{J}_{C-^{117}Sn} = 62.6$ Hz], C-3), 70.1 (C-9), 29.3 ([d], $[^3\mathcal{J}_{C-[Sn]} = 20.3$ Hz], C-7), 27.4 ([d+d], $[^2\mathcal{J}_{C-^{119}Sn} = 54.3$ Hz], $[^2\mathcal{J}_{C-^{117}Sn} = 52.2$ Hz], C-6), 21.6 (C-4), 13.9 (C-8), 9.6 ([d+d], $[^1\mathcal{J}_{C-^{119}Sn} = 343.3$ Hz], $[^1\mathcal{J}_{C-^{117}Sn} = 328.4$ Hz], C-5); HRMS-APCI (*m/z*) found $[M-Bu]^+$ 395.1400, $C_{19}H_{31}O^{120}Sn$ requires 395.1420.

(E)-(3-(benzyloxy)but-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate **541**

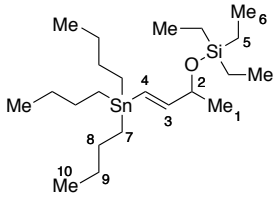


Trimethylsilyltrifluoromethanesulfonate (38 μL, 0.20 mmol) was added at −40 °C to a stirred solution of bis(trifluoroacetoxy)iodobenzene (86 mg, 0.20 mmol) in dichloromethane (1 mL). The mixture was warmed to room temperature then stirred for a further 10 minutes. The yellow mixture was then re-cooled to −40 °C and *(E)-(3-(benzyloxy)but-1-en-1-yl)tributylstannane* **540** (90.2 mg, 200 μmol) was added dropwise as a solution in dichloromethane (1 mL). The resulting solution was warmed to room temperature, stirred for a further 10 minutes and then loaded directly onto a packed silica column. The

crude reaction mixture was purified by silica column chromatography, eluting with 0–50% acetone in dichloromethane, to furnish the title compound as a colourless oil (83.4 mg, 160 µmol, 80%).

IR ν_{max}/cm^{-1} (film): 3063, 2980, 2869, 1670 (C=C), 1445, 1239, 1376, 1224, 1158, 1025, 990; ^{1}H NMR (400 MHz, d_6-acetone) δ (ppm): 8.28–8.25 (m, 2H, H-6), 7.81–7.76 (m, 1H, H-8), 7.66–7.60 (m, 2H, H-7), 7.42 (dd, $\mathcal{J}$ = 13.9, 1.0 Hz, 1H, H-1), 7.34–7.24 (m, 5H, H-11,12,13), 7.15 (dd, $\mathcal{J}$ = 13.9, 6.0 Hz, 1H, H-2), 4.54 (d, $\mathcal{J}$ = 11.9 Hz, 1H, H-9a), 4.48 (d, $\mathcal{J}$ = 11.9 Hz, 1H, H-9b), 4.33 (app. qnd, $\mathcal{J}$ = 6.4, 1.0 Hz, 1H, H-3), 1.29 (d, $\mathcal{J}$ = 6.4 Hz, 3H, H-4); ^{13}C NMR (100 MHz, d_6-acetone) δ (ppm): 154.7 (C-2), 139.1 (C-10), 136.7 (C-6), 133.4 (C-8), 132.9 (C-7), 129.0 (C-12), 128.4 (C-11), 128.3 (C-13), 112.6 (C-5), 101.8 (C-1), 76.7 (C-3), 71.3 (C-9), 20.6 (C-4); ^{19}F NMR (376 MHz, d_6-acetone) *δ*: −78.9; HRMS-ESI (*m/z*) found [M−OTf]$^+$ 365.0387, $C_{17}H_{18}OI$ requires 365.0397.

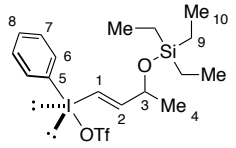
(E)-triethyl((4-(tributylstannyl)but-3-en-2-yl)oxy)silane **542**



Prepared according to general procedure **H** with Pd_2dba_3 (4.6 mg, 5.0 µmol) and tricylohexylphosphonium tetrafluoroborate (7.4 mg, 20 µmol) in toluene (8 mL), di-*iso*-proylethylamine (7.0 µL, 20 µmol), *(but-3-yn-2-yloxy)triethylsilane* **532** (184 mg, 1.00 mmol) in toluene (2 mL), and tributyltin hydride (323 µL, 1.20 mmol) in toluene (3 mL). Purification was carried out by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (176 mg, 0.37 mmol, 37%).

R_F 0.35 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2955, 2925, 2875, 1603, 1458, 1377, 1240, 1127, 1091, 1070, 1003, 984; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.05 (d, $\mathcal{J}$ = 19.0 Hz, 1H, H-4), 5.98 (dd, $\mathcal{J}$ = 19.0, 4.7 Hz, 1H, H-3), 4.26–4.18 (m, 1H, H-2), 1.54–1.42 (m, 6H, H-9), 1.30 (app. sx, $\mathcal{J}$ = 7.3 Hz, 6H, H-8), 1.22 (d, $\mathcal{J}$ = 6.4 Hz, 3H, H-1), 0.95 (t, $\mathcal{J}$ = 7.9 Hz, 9H, H-6), 0.91-0.85 (m, 15H, H-7,10), 0.60 (q, $\mathcal{J}$ = 7.9 Hz, 6H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 152.8 (C-3), 125.4 ([d+d], [$^{1}\mathcal{J}_{C-^{119}Sn}$ = 384.0 Hz], [$^{1}\mathcal{J}_{C-^{117}Sn}$ = 367.0 Hz], C-4), 72.2 ([d], [$^{3}\mathcal{J}_{C-[Sn]}$ = 66.3 Hz], C-2), 29.2 ([d], [$^{3}\mathcal{J}_{C-[Sn]}$ = 20.7 Hz], C-9), 27.4 ([d+d], [$^{2}\mathcal{J}_{C-^{119}Sn}$ = 54.7 Hz], [$^{2}\mathcal{J}_{C-^{117}Sn}$ = 52.2 Hz], C-8), 24.5 (C-1), 13.9 (C-10), 9.5 ([d+d], [$^{1}\mathcal{J}_{C-^{119}Sn}$ = 342.9 Hz], [$^{1}\mathcal{J}_{C-^{117}Sn}$ = 327.6 Hz], C-7), 7.0 (C-6), 5.0 (C-5); HRMS-APCI (*m/z*) found [M−Bu]$^+$ 419.1813, $C_{18}H_{39}OSi^{120}Sn$ requires 419.1795.

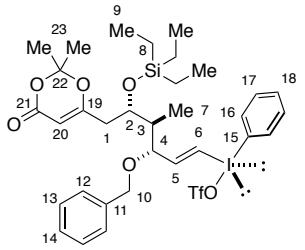
(E)-phenyl(3-((triethylsilyl)oxy)but-1-en-1-yl)iodonium trifluoromethanesulfonate **543**



Triethylsilyltrifluoromethanesulfonate (11 μL, 50 μmol) was added at −40 °C to a stirred solution of bis(trifluoroacetoxy)iodobenzene (22 mg, 50 μmol) in dichloromethane (0.2 mL). The resulting mixture was warmed to room temperature then stirred for a further 10 minutes. The yellow mixture was then re-cooled to −40 °C and *(E)-triethyl((4-(tributylstannyl)but-3-en-2-yl)oxy)silane* **542** (24.0 mg, 50 μmol) was added dropwise as a solution in dichloromethane (0.3 mL). The resulting solution was warmed to room temperature, stirred for a further ten minutes and loaded directly onto a packed silica column. The crude reaction mixture was purified by silica column chromatography, eluting with 0–50% acetone in dichloromethane, to furnish the title compound as a colourless oil (3.2 mg, 5.9 μmol, 12%).

IR ν_{max}/cm^{-1} (film): 2958, 2878, 1473, 1445, 1276, 1241, 1225, 1158, 1098, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.94 (d, J = 8.4 Hz, 2H, H-6), 7.69 (t, J = 7.5 Hz, 1H, H-8), 7.52 (app. t, J = 7.9 Hz, 2H, H-7), 6.92–6.84 (m, 2H, H-1,2), 4.54 (qd, J = 6.5, 2.7 Hz, 1H, H-3), 1.28 (d, J = 6.5 Hz, 3H, H-4), 0.88 (t, J = 7.9 Hz, 9H, H-10), 0.55 (q, J = 7.9 Hz, 6H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 155.6 (C-2), 135.8 (C-6), 133.0 (C-8), 132.6 (C-7), 110.2 (C-5), 99.0 (C-1), 70.2 (C-3), 23.6 (C-4), 6.8 (C-10), 4.8 (C-9); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −79.3; HRMS-ESI (*m/z*) found $[M–OTf]^+$ 365.0387 HRMS-ESI (*m/z*) found $[M–OTf]^+$ 389.0776, $C_{16}H_{26}OSiI$ requires 389.0792.

((3R,4S,5S,E)-3-(benzyloxy)-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-4-methyl-5-((triethylsilyl)oxy)hex-1-en-1-yl)(phenyl)-iodonium trifluoromethanesulfonate **536**

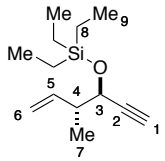


Triethylsilyltrifluoromethanesulfonate (43 μL, 0.20 mmol) was added at −78 °C to a stirred suspension of bis(trifluoroacetoxy)iodobenzene (103 mg, 0.24 mmol) and anhydrous sodium carbonate (127 mg, 1.2 mmol) in dichloromethane (2.5 mL). The resulting mixture was warmed to room temperature and stirred for a further 5 minutes. The reaction mixture was re-cooled to −78 °C and *6-((2S,3S,4R,E)-4-(benzyloxy)-3-methyl-6-(tributylstannyl)-2-((triethylsilyl)oxy)hex-5-en-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **534** (60.0 mg, 80 μmol) was added dropwise as a solution in dichloromethane (2.5 mL). The product suspension was warmed to room temperature and loaded directly onto a packed silica column. The crude reaction

mixture was purified by two rounds of silica column chromatography, eluting with 0–50% acetone in dichloromethane, to furnish the title compound as a yellow oil (5.0 mg, 6.2 μmol, 8%).

^{1}H NMR (500 MHz, d$_3$-MeCN) δ (ppm): 8.05 (d, $\mathcal{J}$ = 7.5 Hz, 2H, H-16), 7.76 (t, $\mathcal{J}$ = 7.5 Hz, 1H, H-18), 7.58 (app. t, $\mathcal{J}$ = 7.5 Hz, 2H, H-17), 7.38–7.29 (m, 3H, H-13,14), 7.25 (d, $\mathcal{J}$ = 6.8 Hz, 2H, H-12), 7.10 (d, $\mathcal{J}$ = 13.8 Hz, 1H, H-6), 6.85 (dd, $\mathcal{J}$ = 13.8, 8.1 Hz, 1H, H-5), 5.23 (s, 1H, H-20), 4.47–4.40 (m, 2H, H-2,10a), 4.31 (d, $\mathcal{J}$ = 11.0 Hz, 1H, H-10b), 3.90 (app.t, $\mathcal{J}$ = 8.6 Hz, 1H, H-4), 2.45–2.39 (m, 2H, H-1), 1.75–1.68 (m, 1H, H-3), 1.58 (s, 3H, H-23a), 1.51 (s, 3H, H-23b), 0.93 (t, $\mathcal{J}$ = 7.8 Hz, 9H, H-9), 0.72 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-7), 0.60–0.54 (m, 6H, H-8); ^{19}F NMR (376 MHz, d$_3$-MeCN) *δ*: −79.3. Further characterisation data could not be obtained due to product instability.

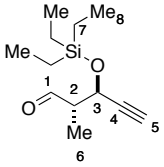
triethyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane **550**



Adapted from a procedure reported by Hiemstra et al.[223] Triethylsilyl chloride (8.59 mL, 51.3 mmol) was added at 0 °C to a stirred solution of imidazole (4.64 mg, 68.4 mmol) and *(3R,4R)-4-methylhex-5-en-1-yn-3-ol* **514** (1.88 g, 17.1 mmol) in dimethylformamide (57 mL). The resulting mixture was warmed to room temperature and was stirred for a further hour before the product mixture was diluted with water (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and sat. aq. $NaHCO_3$ solution (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to prolonged high vacuum (approx. 0.5 mbar, 48 hours) to remove any residual silanol impurities then purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (2.70 g, 12.1 mmol, 71%).

R_F 0.66 (1% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3309 (*sp* C–H), 2956, 2884, 1643 (C=C), 1461, 1415, 1344, 1239, 1080, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.83 (ddd, $\mathcal{J}$ = 17.4, 10.2, 7.3 Hz, 1H, H-5), 5.12–5.04 (m, 2H, H-6), 4.26 (dd, $\mathcal{J}$ = 5.5, 2.1 Hz, 1H, H-3), 2.45–2.35 (m, 2H, H-1,4), 1.11 (d, $\mathcal{J}$ = 6.8 Hz, 3H, H-7), 0.98 (t, $\mathcal{J}$ = 7.9 Hz, 9H, H-9), 0.69–0.61 (m, 6H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.9 (C-5), 115.4 (C-4), 84.0 (C-2), 73.1 (C-1), 66.7 (C-3), 44.9 (C-4), 14.8 (C-7), 6.9 (C-9), 4.9 (C-8); HRMS-ESI (*m/z*) found $[M+H]^+$ 224.1602, $C_{13}H_{24}OSi$ requires 224.1596; $[\alpha]_D^{26}$ = +14.9 ° (c = 1.0, $CHCl_3$).

(2S,3R)-2-methyl-3-((triethylsilyl)oxy)pent-4-ynal **549**



Prepared according to general procedure **F** on a 3.1 mmol scale.

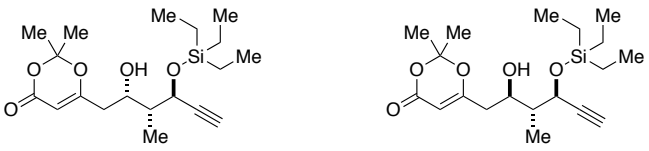
Step F1 was performed with NMO (2.60 mL, 50 wt% in water, 12.5 mmol), OsO_4 (127 µL, 2.5 wt% in *tert*-butanol, 13.0 µmol) and *triethyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane* **550** (0.70 g, 3.13 mmol) with stirring for 72 hours. The resulting solution was quenched with sat. aq. $Na_2S_2O_3$ solution (150 mL) and ethyl acetate (150 mL). Following separation, the aqueous layer was extracted with ethyl acetate (4 x 100 mL) to furnish the crude diol mixture as 2.5:1 mixture of diastereoisomers.

Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.52 (dd, $\mathcal{J}$ = 6.6, 2.1 Hz, 1H, H-3), 3.78–3.52 (m, 3H, H-0,1), 3.38 (br. s, 1H, OH), 2.49 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-5), 2.00–1.90 (m, 1H, H-2), 1.02–0.97 (m, 12H, H-6,8), 0.76–0.61 (m, 6H, H-7). *Minor diastereoisomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.43 (dd, $\mathcal{J}$ = 4.3, 2.1 Hz, 1H, H-3), 4.30–4.24 (m, 1H, H-1), 3.78–3.52 (m, 2H, H-0), 3.10 (br. s, 1H, OH), 2.47 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-5), 1.87–1.79 (m, 1H, H-2), 1.05 (d, $\mathcal{J}$ = 7.1 Hz, 3H, H-6), 1.02–0.97 (m, 9H, H-8), 0.76–0.61 (m, 6H, H-7).

Step F2 was performed with silica-supported sodium *meta*-periodate (31.0 g, approx. 15 wt% $NaIO_4$, 21.7 mmol) in dichloromethane (300 mL). The crude residue was purified by silica column chromatography, eluting with 1–2% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (557 mg, >98% diasteromeric purity, 2.46 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.81 (d, $\mathcal{J}$ = 1.6 Hz, 1H, H-1), 4.60 (dd, $\mathcal{J}$ = 5.9, 2.2 Hz, 1H, H-3), 2.62 (app. qd, $\mathcal{J}$ = 7.1, 1.6 Hz, 1H, H-2), 2.51 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-5), 1.16 (d, $\mathcal{J}$ = 7.1 Hz, 3H, H-6), 0.96 (t, $\mathcal{J}$ = 8.0 Hz, 9H, H-8), 0.73–0.59 (m, 6H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 203.1 (C-1), 83.0 (C-4), 74.7 (C-3) 63.5 (C-5), 52.9 (C-2), 10.4 (C-6), 6.8 (C-8), 4.8 (C-7). Consumed directly.

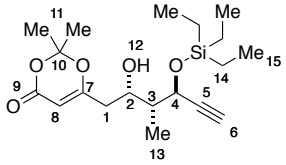
6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **548** and *6-((2R,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **epi-548**



Prepared according to general procedure **G** with *((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane* **459** (4.76 g, 22.2 mmol) in dichloromethane (24 mL), boron trifluoride diethyl etherate (0.57 mL, 4.5 mmol) in dichloromethane (18 mL) and *(2S,3R)-2-methyl-3-((triethylsilyl)oxy)pent-4-*

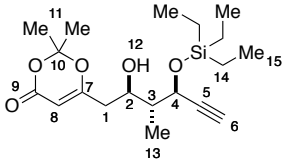
*yna*l **549** (1.05 g, >98% purity, 4.62 mmol) in dichloromethane (45 mL). The reaction mixture was quenched with triethylamine (10 mL) and sat. aq. $NaHCO_3$ solution (40 mL) and the work-up performed with dichloromethane (2 x 100 mL) and brine (50 mL). The crude residue was purified by silica column chromatography, eluting with 10% diethyl ether in petroleum ether 40–60, to give the title compounds in a 5:1 diastereomeric ratio. The mixture of diastereoisomers was further purified by silica column chromatography, eluting with 2–3% diethyl ether in toluene, to furnish the title compound **548** (1.31 g, 3.56 mmol, 77%) and its C-2 epimer **epi-548** (288 mg, 0.78 mmol, 17%), both as colourless oils.

6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **548**



R_F 0.14 (10% Et_2O in PhMe); IR ν_{max}/cm^{-1} (film): 3469 (br., O–H), 3310 (*sp* C–H), 2957, 2912, 2878, 1720 (C=O), 1635 (C=C), 1459, 1391, 1376, 1274, 1204, 1087, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.35 (s, 1H, H-8), 4.59–4.54 (m, 1H, H-2), 4.44 (dd, $\mathcal{J}$ = 4.0, 2.2 Hz, 1H, H-4), 3.12 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-12), 2.50 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-6), 2.45 (dd, $\mathcal{J}$ = 14.6, 8.4 Hz, 1H, H-1a), 2.26 (dd, $\mathcal{J}$ = 14.6, 5.3 Hz, 1H, H-1b), 1.76–1.70 (m, 1H, H-3), 1.69 (s, 3H, H-11a), 1.68 (s, 3H, H-11b), 1.05 (d, $\mathcal{J}$ = 7.4 Hz, 3H, H-13), 0.98 (t, $\mathcal{J}$ = 8.0 Hz, 9H, H-15), 0.75–0.61 (m, 6H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.4 (C-7), 161.3 (C-9), 106.7 (C-10), 95.0 (C-8), 83.8 (C-5), 74.4 (C-6), 68.4 (C-2), 67.7 (C-4) 43.0 (C-3), 39.1 (C-1), 25.4 (C-11a), 25.0 (C-11b), 10.2 (C-13), 6.8 (C-15), 4.7 (C-14); HRMS-ESI (*m/z*) found $[M+Na]^+$ 391.1900, $C_{19}H_{32}O_5SiNa$ requires 391.1911; $[\alpha]_D^{25}$ = +13.2 ° (c = 1.0, $CHCl_3$).

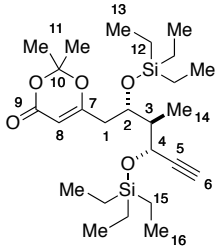
6-((2R,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **epi-548**



R_F 0.11 (10% Et_2O in PhMe); IR ν_{max}/cm^{-1} (film): 3454 (br., O–H), 3310 (*sp* C–H), 2957, 2912, 2878, 1716 (C=O), 1634 (C=C), 1459, 1392, 1377, 1276, 1204, 1080, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.36 (s, 1H, H-8), 4.49 (dd, $\mathcal{J}$ = 6.4, 2.2 Hz, 1H, H-4), 3.93–3.87 (m, 1H, H-2), 3.06 (d, $\mathcal{J}$ = 3.2 Hz, 1H, H-12), 2.56 (ddd, $\mathcal{J}$ = 14.6, 2.9, 0.8 Hz, 1H, H-1a), 2.48 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-6), 2.33 (dd, $\mathcal{J}$ = 14.6, 9.7 Hz, 1H, H-1b), 1.87 (app. sx, 1H, H-3), 1.70 (s, 3H, H-11a), 1.69 (s, 3H, H-11b), 1.01 (d, $\mathcal{J}$ = 6.9 Hz, 3H, H-13), 0.98 (t, $\mathcal{J}$ = 7.9 Hz, 9H, H-15), 0.75–0.61 (m, 6H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.7 (C-7), 161.2 (C-9), 106.7 (C-10), 95.5 (C-8), 83.7 (C-5), 74.4 (C-6), 71.5 (C-2), 66.3 (C-4) 45.5 (C-3), 39.3 (C-1), 25.7 (C-11a), 24.7 (C-11b), 12.6 (C-13), 6.8 (C-15), 4.9 (C-14); HRMS-

ESI (*m/z*) found $[M+Na]^+$ 391.1901, $C_{19}H_{32}O_5SiNa$ requires 391.1911; $[\alpha]_D^{25}$ = +31.0 ° (c = 1.0, $CHCl_3$).

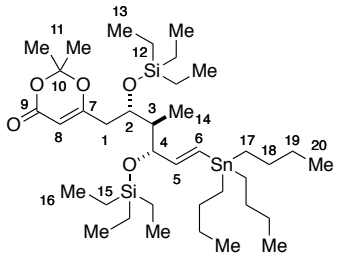
2,2-dimethyl-6-((2S,3R,4R)-3-methyl-2,4-bis((triethylsilyl)oxy)hex-5-yn-1-yl)-4H-1,3-dioxin-4-one **547**



Adapted from a procedure reported by Hiemstra et al.[223] Triethylsilyl chloride (0.76 mL, 4.50 mmol) was added dropwise at 0 °C to a stirred solution of imidazole (408 mg, 6.00 mmol) and *6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **548** (552 mg, 1.50 mmol) in dimethylformamide (5 mL). The resulting mixture was warmed to room temperature and was stirred for 2 hours then diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and sat. aq. $NaHCO_3$ solution (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product residue was subjected to prolonged high vacuum (approx. 0.5 mbar, 24 hours) to remove silanol impurities then purified by silica column chromatography, eluting with 5–10% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (696 mg, 1.44 mmol, 96%).

R_F 0.22 (20% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3310 (*sp* C–H), 2955, 2912, 2877, 1735 (C=O), 1636 (C=C), 1459, 1389, 1374, 1271, 1204, 1078, 1012; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.26 (s, 1H, H-8), 4.32–4.28 (m, 2H, H-2,4), 2.45–2.41 (m, 3H, H-1,6), 1.72 (app. qnd, $\mathcal{J}$ = 7.1, 2.9 Hz, 1H, H-3), 1.68 (s, 3H, H-11a), 1.67 (s, 3H, H-11b), 0.99–0.93 (m, 21 H, H-13,14,16), 0.74–0.56 (m, 12H, H-12,15); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.1 (C-7), 161.2 (C-9), 106.6 (C-10), 95.2 (C-8), 84.7 (C-5), 74.5 (C-6), 68.3 (C-2), 63.8 (C-4) 45.4 (C-3), 40.0 (C-1), 25.9 (C-11a), 24.6 (C-11b), 9.6 (C-14), 7.1 (2C, C-13,16), 5.4 (C-12/15), 5.3 (C-12/15); HRMS-ESI (*m/z*) found $[M+Na]^+$ 505.2790, $C_{25}H_{46}O_5Si_2Na$ requires 505.2776; $[\alpha]_D^{25}$ = +11.6 ° (c = 1.0, $CHCl_3$).

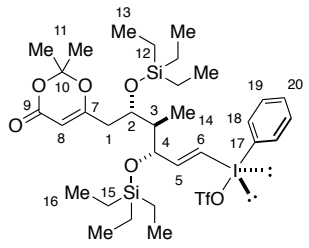
2,2-dimethyl-6-((2S,3R,4R,E)-3-methyl-6-(tributylstannyl)-2,4-bis((triethylsilyl)oxy)hex-5-en-1-yl)-4H-1,3-dioxin-4-one **546**



Prepared according to general procedure **H** with Pd_2dba_3 (2.3 mg, 2.5 μmol) and tricylohexylphosphonium tetrafluoroborate (3.7 mg, 10 μmol) in dichloromethane (4 mL), di-*iso*-proylethylamine (3.5 μL, 10 μmol), *2,2-dimethyl-6-((2S,3R,4R)-3-methyl-2,4-bis((triethylsilyl)oxy)hex-5-yn-1-yl)-4H-1,3-dioxin-4-one* **547** (241 mg, 0.50 mmol) in dichloromethane (1 mL), and tributyltin hydride (162 μL, 0.60 mmol) in dichloromethane (2 mL). Purification was carried out by silica column chromatography, eluting with 5% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (307 mg, 0.40 mmol, 80%).

R_F 0.40 (20% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2955, 2914, 2875, 1739 (C=O), 1636 (C=C), 1459, 1389, 1375, 1270, 1204, 1052, 1015, 742; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.05 ([d+d]dd, $[^2\mathcal{J}_{H-^{119}Sn} = 73.9$ Hz], $[^2\mathcal{J}_{H-^{117}Sn} = 71.7$ Hz], $\mathcal{J} = 18.9$, 0.5 Hz, 1H, H-6), 5.78 ([d+d]dd, $[^3\mathcal{J}_{H-^{119}Sn} = 62.6$ Hz], $[^3\mathcal{J}_{H-^{117}Sn} = 60.3$ Hz], $\mathcal{J} = 18.9$, 7.9 Hz, 1H, H-5), 5.25 (s, 1H, H-8), 4.42 (ddd, $\mathcal{J} = 7.9$, 5.9, 2.1 Hz, 1H, H-2), 3.85 (app. t, $\mathcal{J} = 8.1$ Hz, 1H, H-4), 2.47–2.38 (m, 2H, H-1), 1.68 (s, 3H, H-11a), 1.67 (s, 3H, H-11b), 1.57–1.40 (m, 7H, H-3,19), 1.31 (app. sx, $\mathcal{J} = 7.3$ Hz, 6H, H-18), 0.99–0.86 (m, 33H, H-13,16,17,20), 0.72 (d, $\mathcal{J} = 7.0$ Hz, 3H, H-14), 0.64–0.54 (m, 12H, H-12,15); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.4 (C-7), 161.4 (C-9), 150.4 (C-5), 131.4 ([d+d], $[^1\mathcal{J}_{C-^{119}Sn} = 367.1$ Hz], $[^1\mathcal{J}_{C-^{117}Sn} = 351.1$ Hz], C-6), 106.5 (C-10), 95.1 (C-8), 79.6 ([d], $[^3\mathcal{J}_{C-[Sn]} = 64.6$ Hz], C-4), 68.2 (C-2), 43.7 (C-3), 40.7 (C-1), 29.3 ([d], $[^3\mathcal{J}_{C-[Sn]} = 20.8$ Hz], C-19), 27.4 ([d], $[^2\mathcal{J}_{C-[Sn]} = 53.9$ Hz], C-18), 26.0 (C-11a), 24.6 (C-11b), 13.8 (C-20), 9.5 ([d+d], $[^1\mathcal{J}_{C-^{119}Sn} = 343.6$ Hz], $[^1\mathcal{J}_{C-^{117}Sn} = 328.7$ Hz], C-17), 9.4 (C-14), 7.2 (C-13/16), 7.1 (C-13/16), 5.8 (C-12/15), 5.5 (C-12/15); HRMS-ESI (*m/z*) found $[M+Na]^+$ 797.3975, $C_{37}H_{74}O_5Si_2{}^{120}SnNa$ requires 505.2776; $[\alpha]_D^{25} = +16.3$ ° (c = 1.0, $CHCl_3$).

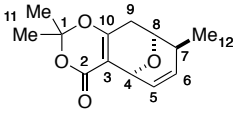
((3R,4R,5S,E)-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-4-methyl-3,5-bis((triethylsilyl)oxy)hex-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate **531**



Triethylsilyltrifluoromethanesulfonate (34 µL, 0.15 mmol) was added at −78 °C to a stirred solution of bis(trifluoroacetoxy)iodobenzene (64.5 mg, 0.15 mmol) and di-*tert*-butyl pyridine (34 µL, 0.15 mmol) in dichloromethane (1 mL). The mixture was warmed to room temperature and stirred for 5 minutes then re-cooled to −78 °C and *2,2-dimethyl-6-((2S,3R,4R,E)-3-methyl-6-(tributylstannyl)-2,4-bis((triethylsilyl)oxy)hex-5-en-1-yl)-4H-1,3-dioxin-4-one* **546** (39.0 mg, 80 µmol) added dropwise as a solution in dichloromethane (1.5 mL). The resulting suspension was warmed to room temperature and quenched with water (2 mL). The layers were separated, and the aqueous extracted with dichloromethane (2 x 1 mL). The organics were combined, dried over anhydrous $MgSO_4$ and loaded directly onto a packed silica column. The crude reaction mixture was purified by silica column chromatography, eluting with 0–100% acetonitrile in dichloromethane then 100% acetone, to furnish the title compound as a colourless oil (32.1 mg, 38 µmol, 76%).

^{1}H NMR (400 MHz, d_3-MeCN) δ (ppm): 8.04 (d, J = 7.5 Hz, 2H, H-18), 7.76 (t, J = 7.4 Hz, 1H, H-20), 7.58 (app. t, J = 7.9 Hz, 2H, H-19), 6.99–6.97 (m, 2H, H-5,6), 5.25 (s, 1H, H-8), 4.32–4.25 (m, 2H, H-2,4), 2.44 (app. d, J = 7.1 Hz, 2H, H-1), 1.72–1.66 (m, 1H, H-3), 1.64 (s, 3H, H-11a), 1.63 (s, 3H, H-11b), 0.96 (t, J = 7.9 Hz, 9H, H-13/16), 0.85 (t, J = 7.9 Hz, 9H, H-16/13), 0.71 (d, J = 7.0 Hz, 3H, H-14), 0.62 (q, J = 7.9 Hz, 6H, H-12/15), 0.50 (q, J = 7.9 Hz, 6H, H-15/12); ^{19}F NMR (376 MHz, d_3-MeCN) δ: −77.3. Further characterisation data could not be obtained due to product instability.

(5S,8S,9S)-2,2,8-trimethyl-5,8,9,10-tetrahydro-4H-5,9-epoxycycloocta[d][1,3]dioxin-4-one **552**



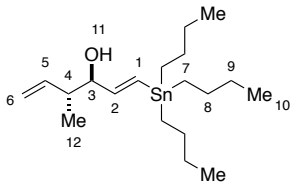
Prepared according to a procedure adapted from Gaunt et al.[158] *((3R,4R,5S,E)-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-4-methyl-3,5-bis((triethylsilyl)oxy)hex-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate* **531** (60 mg, ~50% purity [desilylated iodonium salt impurities], 70 µmol) in dichloromethane (1.5 mL) was added at 0 °C to a solution of *(E)-pent-3-en-1-yl dimethylcarbamate* **317** (7.9 mg, 50 µmol) and $(CuOTf)_2$•PhH (2.5 mg, 5 µmol) in dichloromethane (1 mL), The resulting green solution was stirred at 0 °C for 30 minutes then at 35 °C for 6 hours before the reaction was quenched by the addition of triethylamine (0.5 mL) and sat aq. $NaHCO_3$ (5 mL) and stirred vigorously. The phases were separated and the organic phase

was filtered through a plug of anhydrous Na_2SO_4 then concentrated under a stream of nitrogen gas. The resulting residue was purified by two rounds of silica column chromatography, eluting first with 10–40% ethyl acetate in petroleum ether 40–60 and secondly with 0–20% acetonitrile in dichloromethane, to furnish the title compound an orange oil (4.1 mg, 17 μmol, 24%).

R_F 0.22 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2960, 2933, 2857, 1724 (C=O), 1659 (C=C), 1409, 1391, 1378, 1272, 1269, 1203, 1117, 1063, 990; ^{1}H NMR (500 MHz, d_3-MeCN) δ (ppm): 5.88 (ddd, $\mathcal{J}$ = 10.1, 3.8, 2.9 Hz, 1H, H-6), 5.57 (app. ddt, $\mathcal{J}$ = 10.1, 2.0, 1.0 Hz, 1H, H-5), 4.84 (d, $\mathcal{J}$ = 3.9 Hz, 1H, H-4), 4.43 (dd, $\mathcal{J}$ = 8.6, 6.3, 1H, H-8), 2.88–2.80 (m, 1H, H-7), 2.62 (dd, $\mathcal{J}$ = 19.7, 8.6 Hz, 1H, H-9a), 2.27 (dd, $\mathcal{J}$ = 19.7, 0.9 Hz, 1H, H-9b), 1.67 (s, 3H, H-11a), 1.62 (s, 3H, H-11b), 0.93 (d, $\mathcal{J}$ = 7.5 Hz, 3H, H-12); ^{13}C NMR (125 MHz, d_3-MeCN) δ (ppm): 165.5 (C-10), 159.4 (C-2), 129.1 (C-6), 128.9 (C-5), 108.2 (C-3), 107.6 (C-1), 70.7 (C-8), 63.8 (C-4), 33.9 (C-7), 26.3 (C-9), 25.7 (C-11a), 24.7 (C-11b), 16.3 (C-12); HRMS-ESI (*m/z*) found $[M+Na]^+$ 259.0941, $C_{13}H_{16}O_4Na$ requires 259.0941; $[\alpha]_D^{25}$ = −100.0 ° (c = 0.1, MeCN).

6.3.5. Third generation approach

(3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-ol **562**

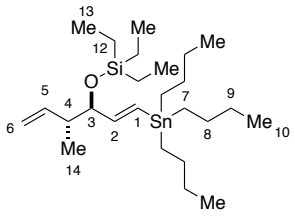


Adapted from a procedure reported by Krische et al.[190] Tetrahydrofuran (0.2 mL) and 3-buten-2-yl acetate (101 μL, 0.80 mmol) were sequentially added to an oven-dried, sealed microwave tube charged with $[Ir(cod)Cl]_2$ (6.7 mg, 10 μmol), (*R*)-SegPhos (12.2 mg, 20 μmol), Cs_2CO_3 (26.1 mg, 80 μmol), 4-cyano-3-nitrobenzoic acid (7.7 mg, 40 μmol) under an atmosphere of nitrogen. The resulting mixture was heated at 90 °C for 30 minutes and then cooled to room temperature before undergoing the addition of *(E)-3-(tributylstannyl)prop-2-en-1-ol* **561** (139.2 mg, 0.40 mmol) in tetrahydrofuran (0.2 mL). The suspension was then heated to 90 °C and stirred for 48 hours before being cooled back to room temperature. The crude reaction mixture was then filtered through a plug of silica, eluting with ethyl acetate, and concentrated *in vacuo*. The resulting residues were purified by two rounds of silica column chromatography, eluting firstly with 2% ethyl acetate in petroleum ether 40–60 and secondly in 1% ethyl acetate in petroleum ether, to furnish the title compound in 6:1 ratio of diastereoisomers and as a pale yellow oil (28.9 mg, 0.072 mmol, 18%).

R_F 0.36 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3381 (br., O–H), 2957, 2925, 2872, 2853, 1640 (C=C), 1602, 1457, 1377, 1340, 1292, 1183, 1072, 990; *Major diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.17 ([d+d]dd, [$^2\mathcal{J}_{H-^{119}Sn}$ = 72.4 Hz], [$^2\mathcal{J}_{H-^{117}Sn}$ = 69.5 Hz], $\mathcal{J}$ = 19.1, 1.2 Hz, 1H, H-1 [obscured]), 5.93 ([d+d]dd, [$^3\mathcal{J}_{H-^{119}Sn}$ = 63.7 Hz], [$^3\mathcal{J}_{H-^{117}Sn}$ = 61.0 Hz], $\mathcal{J}$ = 19.1, 5.9 Hz, 1H, H-2

[obscured]), 5.76 (ddd, $\mathcal{J}$ = 17.8, 10.0, 7.3 Hz, 1H, H-5 [obscured]), 5.15–5.13 (m, 1H, H-6a), 5.12–5.10 (m, 1H, H-6b [obscured]), 3.88–3.82 (m, 1H, H-3), 2.29 (app. sx, $\mathcal{J}$ = 7.0 Hz, 1H, H-4), 1.73 (d, $\mathcal{J}$ = 3.3 Hz, 1H, H-11), 1.55–1.44 (m, 6H, H-8 [obscured]), 1.30 (app. sx, $\mathcal{J}$ = 7.3 Hz, 1H, H-9 [obscured]), 1.01 (d, $\mathcal{J}$ = 6.9 Hz, 3H, H-12 [obscured]), 0.97–0.81 (m, 15H, H-7,10 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.7 (C-2), 140.4 (C-5), 130.1 ([d+d], [$^1\mathcal{J}_{C-^{119}Sn}$ = 369.7 Hz], [$^1\mathcal{J}_{C-^{117}Sn}$ = 353.7 Hz], C-1), 116.4 (C-6), 78.9 ([d], [$^3\mathcal{J}_{C-[Sn]}$ = 61.4 Hz], C-3), 44.2 (C-4), 29.3 ([d], [$^3\mathcal{J}_{C-[Sn]}$ = 20.8 Hz], C-9), 27.4 ([d], [$^2\mathcal{J}_{C-[Sn]}$ = 53.8 Hz], C-8), 16.0 (C-12), 13.9 (C-10), 9.7 ([d+d], [$^1\mathcal{J}_{C-^{119}Sn}$ = 344.7 Hz], [$^1\mathcal{J}_{C-^{117}Sn}$ = 328.7 Hz], C-7); *Minor diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.16 (dd, $\mathcal{J}$ = 19.2, 1.3 Hz, 1H, H-1 [obscured]), 5.99 (dd, $\mathcal{J}$ = 19.2, 5.3 Hz, 1H, H-2 [obscured]), 5.83–5.74 (m, 1H, H-5 [obscured]), 5.11–5.09 (m, 1H, H-6a [obscured]), 5.08–5.07 (m, 1H, H-6b), 4.01 (app. q, $\mathcal{J}$ = 4.6 Hz, 1H, H-3), 2.38 (app. sx, $\mathcal{J}$ = 6.7 Hz, 1H, H-4), 1.63 (d, $\mathcal{J}$ = 5.4 Hz, 1H, H-11), 1.55–1.44 (m, 6H, H-8 [obscured]), 1.30 (app. sx, $\mathcal{J}$ = 7.3 Hz, 1H, H-9 [obscured]), 1.02 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-12 [obscured]), 0.97–0.81 (m, 15H, H-7,10 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.4 (C-2), 140.4 (C-5), 129.1 (C-1), 115.8 (C-6), 78.2 (C-3), 43.7 (C-4), 29.3 (C-9), 27.4 (C-8), 14.8 (C-12), 13.9 (C-10), 9.7 (C-7); HRMS-ESI (*m/z*) found $[M+H]^+$ 403.2019, $C_{19}H_{39}SnO$ requires 403.2021; $[\alpha]_D^{25}$ = −2.3 ° (c = 0.75, $CHCl_3$); HPLC analysis (OD, 0.2% *i*-PrOH in *n*-hexane, 1 mL/min, 218 nm) indicated 18% *e.e.*: t_R (major) = 6.42 minutes, t_R (minor) = 7.10 minutes.

triethyl(((3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-yl)oxy)silane **563**

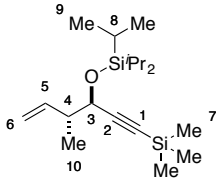


Triethylsilyl trifluoromethanesulfonate (13.4 µL, 68 µmol) was added at −78 °C to a solution of *(3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-ol* **562** (6:1 *d.r.*, 24.9 mg, 62 µmol) and 2,6-lutidine (14.4 µL, 0.12 mmol) in dichloromethane (0.5 mL). The resulting solution was stirred at −78 °C for 30 minutes then warmed to room temperature and stirred for a further two hours. The reaction mixture was quenched on the addition of sat. aq. $NaHCO_3$ solution (0.5 mL). The phases were separated and the aqueous layer extracted with diethyl ether (3 x 1 mL). The combined organic layers were filtered through a plug of anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude residues were purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound in a 6:1 ratio of diasteroisomers and as a colourless oil (24.0 mg, 47 µmol, 76%).

R_F 0.43 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2956, 2928, 2875, 1459, 1417, 1377, 1342, 1238, 1116, 1071, 1005, 992; *Major diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.03 (dd, $\mathcal{J}$ = 19.1, 0.6 Hz, 1H, H-1 [obscured]), 5.90 (dd, $\mathcal{J}$ = 19.1, 6.3 Hz, 1H, H-2 [obscured]), 5.86–5.76 (m, 1H, H-5), 5.03–5.94 (m, 2H, H-6 [obscured]), 3.91–3.86 (m, 1H, H-3 [obscured]), 2.25 (app. sx, $\mathcal{J}$ = 6.7 Hz, 1H,

H-4 [obscured]), 1.54–1.40 (m, 6H, H-8), 1.30 (m, 6H, H-9 [obscured]), 0.98–0.84 (m, 27H, H-7,10,13,14 [obscured]), 0.58 (q, $\mathcal{J}$ = 7.7 Hz, 6H, H-12 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.9 (C-2), 141.3 (C-5), 128.5 ([d+d], [$^{1}\mathcal{J}_{C-^{119}Sn}$ = 380.6 Hz], [$^{1}\mathcal{J}_{C-^{117}Sn}$ = 363.6 Hz], C-1), 114.2 (C-6), 80.6 ([d], [$^{3}\mathcal{J}_{C-[Sn]}$ = 65.1 Hz], C-3), 44.6 (C-4), 29.3 ([d], [$^{3}\mathcal{J}_{C-[Sn]}$ = 21.1 Hz], C-9), 27.4 ([d+d], [$^{2}\mathcal{J}_{C-^{119}Sn}$ = 53.9 Hz], [$^{2}\mathcal{J}_{C-^{117}Sn}$ = 52.2 Hz], C-8), 15.5 (C-14), 13.9 (C-7), 9.6 ([d+d], [$^{1}\mathcal{J}_{C-^{119}Sn}$ = 342.5 Hz], [$^{1}\mathcal{J}_{C-^{117}Sn}$ = 327.2 Hz], C-10), 7.1 (C-12), 5.1 (C-13); *Minor diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.01 (d, $\mathcal{J}$ = 19.2 Hz, 1H, H-1 [obscured]), 5.89 (dd, $\mathcal{J}$ = 19.2, 6.2 Hz, 1H, H-2 [obscured]), 5.86–5.76 (m, 1H, H-5), 5.03–5.94 (m, 2H, H-6 [obscured]), 3.91–3.86 (m, 1H, H-3 [obscured]), 2.25 (app. sx, $\mathcal{J}$ = 6.7 Hz, 1H, H-4 [obscured]), 1.54–1.40 (m, 6H, H-8), 1.30 (m, 6H, H-9 [obscured]), 0.98–0.84 (m, 27H, H-7,10,13,14 [obscured]), 0.58 (q, $\mathcal{J}$ = 7.7 Hz, 6H, H-12 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.0 (C-2), 141.3 (C-5), 128.4 (C-1), 114.1 (C-6), 80.7 (C-3), 44.4 (C-4), 29.3 (C-9), 27.4 (C-8), 15.2 (C-14), 13.9 (C-7), 9.6 (C-10), 7.1 (C-12), 5.1 (C-13); HRMS-ASAP (*m/z*) found [M–Bu]$^+$ 459.2122, $C_{21}H_{43}OSiSn$ requires 455.2108; [α] $^{25}_D$ = –2.0 ^{o} (c = 0.6, $CHCl_3$).

triisopropyl(((3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-yl)oxy)silane **565**

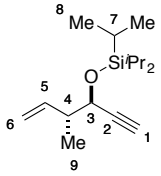


Tri-*iso*-propylsilyl trifluoromethanesulfonate (4.39 mL, 24.0 mmol) was added dropwise at 0 °C to a solution of *(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol* **511** (3.64 g, 20.0 mmol) and 2,6-lutidine (4.54 mL, 24.0 mmol) in dichloromethane (50 mL). The resulting reaction mixture was warmed to room temperature and stirred for 24 hours. Incomplete conversion was observed and so the reaction mixture was cooled back to 0 °C and further portions of 2,6-lutidine (4.54 mL, 24.0 mmol) and tri-*iso*-propylsilyl trifluoromethanesulfonate (4.39 mL, 24.0 mmol) were added. The resulting suspension was warmed to room temperature and was stirred for a further 24 hours. The reaction was quenched with the addition of sat. aq. $NaHCO_3$ solution (50 mL) and the layers were separated. The aqueous layer was extracted with further portions of dichloromethane (2 x 50 mL) before the the organic layers were combined and washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residues were purified by silica column chromatography, eluting with 100% petroleum ether 40–60, then by two rounds of kugelrohr distillation to furnish the title compound as a colourless oil (6.54 g, 19.3 mmol, 97%).

R_F 0.62 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2944, 2893, 2867, 2175 (C≡C), 1644 (C=C), 1463, 1419, 1384, 1371, 1342, 1250, 1090, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.83 (ddd, $\mathcal{J}$ = 17.5, 10.2, 7.5 Hz, 1H, H-5), 5.10–5.00 (m, 2H, H-6), 4.36 (d, $\mathcal{J}$ = 5.2 Hz, 1H, H-3), 2.42 (app. sx, $\mathcal{J}$ = 6.6 Hz, 1H, H-4), 1.13–1.05 (m, 24H, H-8,9,10), 0.15 (s, 9H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ

(ppm): 140.4 (C-5), 115.1 (C-6), 106.2 (C-2), 89.8 (C-1), 67.6 (C-3), 45.3 (C-4), 18.2 (C-9), 14.8 (C-10), 12.5 (C-8), −0.1 (C-7); HRMS-ASAP (*m/z*) found $[M+H]^+$ 339.2526, $C_{19}H_{39}OSi_2$ requires 339.2539; $[\alpha]_D^{25}$ = +7.2 ° (c = 1.0, $CHCl_3$).

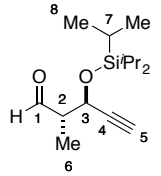
triisopropyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane **566**



To a solution of *triisopropyl(((3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-yl)oxy)silane* **565** (6.10 g, 18.0 mmol) in methanol (90 mL) was added potassium carbonate (24.0 g, 180 mmol) and the resulting cloudy suspension stirred for 45 minutes. The resulting mixture was then filtered through celite™ and the pad washed with diethyl ether (200 mL) and water (100 mL). The phases were separated and the aqueous layer was then extracted with further portions of diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by kugelrohr distillation to furnish the title compound as a colourless oil (4.44 g, 16.6 mmol, 92%).

R_F 0.52 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3311 (*sp* C–H), 2964, 2944, 2867, 1643 (C=C), 1463, 1384, 1371, 1345, 1249, 1092, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 (ddd, $\mathcal{J}$ = 17.5, 10.2, 7.4 Hz, 1H, H-5), 5.13–5.04 (m, 2H, H-6), 4.42 (dd, $\mathcal{J}$ = 4.9, 2.1 Hz, 1H, H-3), 2.46 (app. sx, $\mathcal{J}$ = 6.5 Hz, 1H, H-4), 2.37 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-1), 1.16–1.06 (m, 24H, H-7,8,9); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (C-5), 115.4 (C-6), 83.9 (C-2), 73.2 (C-1), 67.1 (C-3), 45.1 (C-4), 18.20 (C-8), 18.18 (C-8'), 14.3 (C-9), 12.4 (C-7); HRMS-EI (*m/z*) found M^+ 266.2070 $C_{16}H_{30}OSi$ requires 266.2066; $[\alpha]_D^{25}$ = +6.3 ° (c = 1.0, $CHCl_3$).

(2S,3R)-2-methyl-3-((triisopropylsilyl)oxy)pent-4-ynal **567**



Prepared according to general procedure **F** on a 5.0 mmol scale.

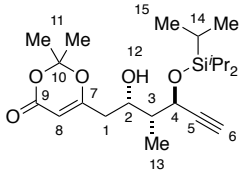
Step F1 was performed with NMO (4.12 mL, 50 wt% in water, 20.0 mmol), OsO_4 (200 µL, 2.5 wt% in *tert*-butanol, 20.0 µmol) and *triisopropyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane* **566** (1.33 g, 5.00 mmol) with stirring for 72 hours. The resulting solution was quenched with sat. aq. $Na_2S_2O_3$ solution (250 mL) and ethyl acetate (250 mL). Following separation, the aqueous layer was extracted with ethyl acetate (5 x 100 mL), and the combined organic layers washed with brine (200 mL), dried over $Na_2S_2O_4$ and concentrated *in vacuo* to furnish the crude diol mixture as 3:1 mixture of diastereoisomers.

Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.77 (dd, $\mathcal{J}$ = 5.3, 2.1 Hz, 1H, H-3), 3.78–3.52 (m, 3H, H-0,1), 3.78 (dd, $\mathcal{J}$ = 11.0, 2.9 Hz, H-0a), 3.74–3.64 (m, 1H, H-1 [obscured]), 3.57 (dd, $\mathcal{J}$ = 11.0, 6.6 Hz, 1H, H-0b), 2.94 (br. s, 1H, O–H), 2.44 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-5), 2.42 (br. s, 1H, O–H), 2.02–1.89 (m, 2H, H-2,O–H), 1.13–1.04 (m, 21H, H-7,8 [obscured]), 1.01 (d, $\mathcal{J}$ = 6.8 Hz, H-6). *Minor diastereoisomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.58 (dd, $\mathcal{J}$ = 3.8, 2.1 Hz, 1H, H-3), 4.28 (ddd, $\mathcal{J}$ = 7.7, 4.0, 2.7 Hz, 1H, H-1), 3.74–3.64 (m, 2H, H-0 [obscured]), 3.04 (br. s, 1H, O–H), 2.50 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-5), 2.42 (br. s, 1H, O–H), 1.89–1.80 (m, 1H, H-2), 1.13–1.04 (m, 24H, H-6,7,8 [obscured]).

Step F2 was performed with silica-supported sodium *meta*-periodate (50.0 g, approx. 15 wt% $NaIO_4$, 35.0 mmol) in dichloromethane (500 mL). The crude residue was purified by silica column chromatography, eluting with 1% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (1.033 g, >98% diasteromeric purity, 3.84 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.84 (d, $\mathcal{J}$ = 1.6 Hz, 1H, H-1), 4.77 (dd, $\mathcal{J}$ = 5.4, 2.2 Hz, 1H, H-3), 2.66 (qdd, $\mathcal{J}$ = 7.1, 5.4, 1.6 Hz, 1H, H-2), 2.52 (d, $\mathcal{J}$ = 2.2 Hz, 1H, H-5), 1.22 (d, $\mathcal{J}$ = 7.1 Hz, 3H, H-6), 1.18–1.11 (m, 3H, H-7), 1.08 (t, $\mathcal{J}$ = 6.4 Hz, 18 H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 203.2 (C-1), 83.0 (C-4), 74.9 (C-5), 63.8 (C-3), 53.3 (C-2), 18.15 (C-8), 18.13 (C-8'), 12.4 (C-8), 10.3 (C-6). Consumed directly.

6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triisopropylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **568**

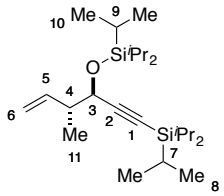


Prepared according to general procedure **G** with *((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane* **459** (5.36 g, 25.0 mmol) in dichloromethane (20 mL), boron trifluoride diethyl etherate (0.75 mL, 5.9 mmol) in dichloromethane (30 mL) and *(2S,3R)-2-methyl-3-((triisopropylsilyl)oxy)pent-4-ynal* **567** (1.01 g, >98% purity, 3.75 mmol) in dichloromethane (50 mL). The reaction mixture was quenched with triethylamine (10 mL) and sat. aq. $NaHCO_3$ solution (40 mL) and the work-up performed with dichloromethane (2 x 100 mL) and brine (50 mL). Excess 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one was removed by kugelrohr distillation and the resulting crude residue was purified by silica column chromatography, eluting with 0–3% diethyl ether in toluene to furnish the title compound together with its C-2 epimer in a 4:1 diastereomeric ratio as a colourless oil (95% purity, 1.49 g, 3.62 mmol, 97%).

R_F 0.16 (10% Et_2O in PhMe); IR ν_{max}/cm^{-1} (film): 3456 (br., O–H), 3311 (*sp* C–H), 2945, 2868, 1722 (C=O), 1636 (C=C), 1463, 1391, 1378, 1274, 1255, 1205, 1093, 1015; *Major diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.32 (s, 1H, H-8 [obscured]), 4.58–4.52 (m, 2H, H-2,4), 3.05 (br. s, 1H, H-12), 2.50 (d, $\mathcal{J}$ = 2.1 Hz, 1H, H-6), 2.44 (dd, $\mathcal{J}$ = 14.5, 8.7 Hz, 1H, H-1a [obscured]), 2.25 (dd, $\mathcal{J}$ = 14.5,

5.3 Hz, 1H, H-1b [obscured]), 1.75–1.69 (m, 1H, H-3), 1.68–1.62 (m, 6H, H-11 [obscured]), 1.19–0.99 (m, 24H, H-13,14,15 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.3 (C-7), 161.2 (C-9), 106.6 (C-10), 94.9 (C-8), 83.8 (C-5), 74.8 (C-6), 68.3 (C-2), 67.9 (C-4), 43.5 (C-3), 39.1 (C-1), 25.3 (C-11a), 24.9 (C-11b), 18.1 (C-15), 12.3 (C-14), 10.0 (C-13); *Minor diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.32 (s, 1H, H-8 [obscured], 4.71 (dd, $\mathcal{J}$ = 5.1, 2.1 Hz, 1H, H-4), 3.87 (app. t, $\mathcal{J}$ = 8.1 Hz, 1H, H-2), 2.80 (br. s, 1H, H-12), 2.56 (dd, $\mathcal{J}$ = 14.7, 2.4 Hz, 1H, H-1a), 2.44–2.42 (m, 1H, H-6 [obscured]), 2.29 (dd, $\mathcal{J}$ = 14.7, 9.4 Hz, 1H, H-1b [obscured]), 1.93–1.83 (m, 1H, H-3), 1.68–1.62 (m, 6H, H-11 [obscured]), 1.19–0.99 (m, 24H, H-13,14,15 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.7 (C-7), 161.1 (C-9), 106.7 (C-10), 95.4 (C-8), 83.4 (C-5), 74.3 (C-6), 70.8 (C-2), 65.4 (C-4), 46.0 (C-3), 39.2 (C-1), 25.6 (C-11a), 24.6 (C-11b), 18.1 (C-15), 12.3 (C-14), 11.6 (C-13); HRMS-ESI (*m/z*) found $[M+Na]^+$ 433.2375, $C_{22}H_{38}O_5SiNa$ requires 433.2381; $[\alpha]_D^{25}$ = +12.3 ° (c = 1.0, $CHCl_3$).

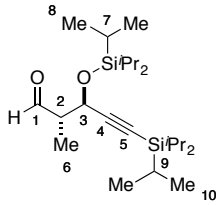
triisopropyl(((3R,4R)-4-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl)oxy)silane **569**



n-Butyllithium (1.6 M in hexanes, 5.84 mL, 9.34 mmol) was added dropwise at −78 °C to a solution of *triisopropyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane* **566** (2.27 g, 8.50 mmol) in diethyl ether (42 mL). The resulting solution was warmed to −40 °C and stirred for one hour before undergoing the dropwise addition of tri-*iso*-propylsilyl triflurometh anesulfonate (2.52 mL, 9.35 mmol). The reaction mixture was then warmed to room temperature and stirred for a further 16 hours. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution (25 mL), the layers separated, and the aqueous layer extracted with further portions of diethyl ether (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residues were purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (3.50 g, 8.30 mmol, 98%).

R_F 0.84 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2943, 2866, 1644 (C=C), 1463, 1384, 1368, 1343, 1246, 1091, 1066, 1015, 995; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 (ddd, $\mathcal{J}$ = 17.5, 10.1, 7.6, 1H, H-5), 5.12–4.98 (m, 2H, H-6), 4.44 (d, $\mathcal{J}$ = 4.8, 1H, H-3), 2.45 (app. sx, $\mathcal{J}$ = 6.5 Hz, 1H, H-4), 1.16–1.05 (m, 45H, H-7,8,9,10,11); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.4 (C-5), 115.1 (C-6), 107.7 (C-2), 85.7 (C-1), 67.7 (C-3), 45.6 (C-4), 18.7 (C-10), 18.2 (C-8), 14.4 (C-11), 12.5 (C-7), 11.4 (C-9); HRMS-ESI (*m/z*) found $[M+NH_4]^+$ 440.3739, $C_{25}H_{54}OSi_2N$ requires 440.3738; $[\alpha]_D^{25}$ = +7.5 ° (c = 1.0, $CHCl_3$).

(2S,3R)-2-methyl-5-(triisopropylsilyl)-3-((triisopropylsilyl)oxy)pent-4-ynal **570**



Performed according to general procedure **F** on a 0.9 mmol scale.

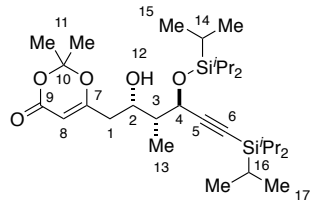
Step F1 was performed with NMO (0.74 mL, 50 wt% in water, 3.6 mmol), OsO_4 (90 µL, 2.5 wt% in *tert*-butanol, 9.0 µmol) and *triisopropyl(((3R,4R)-4-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl)oxy)silane* **566** (379 mg, 900 µmol) with stirring for 144 hours. The resulting solution was quenched with sat. aq. $Na_2S_2O_3$ solution (75 mL) and ethyl acetate (75 mL). Following separation, the aqueous layer was extracted with ethyl acetate (4 x 50 mL) and the combined organic layers washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to furnish the crude diol mixture as 3:1 mixture of diastereoisomers.

Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.75 (d, J = 5.4, 1H, H-3), 3.77 (dd, J = 10.9, 3.1 Hz, 1H, H-0a), 3.72–3.60 (m, 1H, H-1 [obscured]), 3.5 (dd, J = 10.9, 6.2 Hz, 1H, H-0b [obscured]), 3.08 (br. s, 1H, O–H), 2.01–1.92 (m, 1H, H-2), 1.57 (br. s, 1H, O–H [obscured]), 1.27–1.04 (m, 42H, H-7,8,9,10 [obscured]), 1.02 (d, J = 6.8 Hz, H-6 [obscured]. *Minor diastereoisomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.61 (d, J = 3.8 Hz, 1H, H-3), 4.27 (ddd, J = 7.7, 4.2, 2.8 Hz, 1H, H-1), 3.74–3.64 (m, 2H, H-0a,O–H [obscured]), 3.59–3.53 (m, 1H, H-0b [obscured], 2.44 (br. s, 1H, O–H), 1.90–1.83 (m, 1H, H-2), 1.27–1.04 (m, 42H, H-7,8,9,10 [obscured]), 1.02 (d, J = 6.8 Hz, H-6 [obscured].

Step F2 was performed with silica-supported sodium *meta*-periodate (10.0 g, approx. 15 wt% $NaIO_4$, 7.0 mmol) in dichloromethane (100 mL). The crude residue was purified by silica column chromatography, eluting with 0.5% diethyl ether in petroleum ether 40–60 to furnish the title compound as a colourless oil (333 mg, >98% diasteromeric purity, 0.78 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.87 (d, J = 1.6 Hz, 1H, H-1), 4.78 (d, J = 5.3 Hz, 1H, H-3), 2.66 (qdd, J = 6.9, 5.3, 1.6 Hz, 1H, H-2), 1.25–1.10 (m, 9H, H-6,7,9), 1.10–1.05 (m, 36H, H-8,10); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 203.5 (C-1), 106.5 (C-4), 88.0 (C-5), 64.5 (C-3), 53.8 (C-2), 18.65 (C-8), 18.64 (C-8'), 18.20 (C-10), 18.18 (C-10'), 12.5 (C-9), 11.3 (C-7), 10.3 (C-6). Consumed directly.

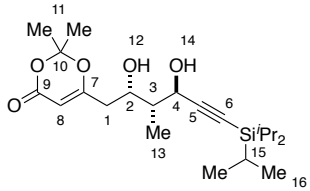
6-((2S,3R,4R)-2-hydroxy-3-methyl-6-(triisopropylsilyl)-4-((triisopropylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **571**



Performed according to general procedure **G** with *((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane* **459** (0.80 g, 3.71 mmol) in dichloromethane (4 mL), boron trifluoride diethyl etherate (111 µL, 0.88 mmol) in dichloromethane (6 mL) and *(2S,3R)-2-methyl-5-(triisopropylsilyl)-3-((triisopropylsilyl)oxy)pent-4-ynal* **570** (313 mg, >98% purity, 0.74 mmol) in dichloromethane (10 mL). The reaction mixture was quenched with triethylamine (2 mL) and sat. aq. $NaHCO_3$ solution (10 mL) and the work-up performed with dichloromethane (2 x 20 mL) and brine (20 mL). Excess 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one was removed by kugelrohr distillation and the resulting crude residue was purified by silica column chromatography, eluting with 0–2.5% diethyl ether in toluene, to furnish the title compound together with its C-2 epimer in a 6:1 diastereomeric ratio and as a colourless oil (376 mg, 0.66 mmol, 89%).

R_F 0.22 (10% Et_2O in PhMe); IR ν_{max}/cm^{-1} (film): 3455 (br., O–H), 2944, 2892, 2867, 1721 (C=O), 1637 (C=C), 1463, 1390, 1378, 1274, 1255, 1206, 1096, 1015; *Major diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.33 (s, 1H, H-8), 4.65–4.61 (m, 1H, H-2), 4.60 (d, $\mathcal{J}$ = 3.6 Hz, 1H, H-4), 3.13 (br. s, 1H, H-12), 2.44 (dd, $\mathcal{J}$ = 14.4, 9.7 Hz, 1H, H-1a), 2.21 (dd, $\mathcal{J}$ = 14.4, 3.8 Hz, 1H, H-1b [obscured]), 1.76–1.70 (m, 1H, H-3 [obscured]), 1.66 (app. s, 6H, H-11 [obscured]), 1.25–0.93 (m, 45H, H-13,14,15,16,17 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.5 (C-7), 161.2 (C-9), 107.5 (C-5), 106.6 (C-10), 95.2 (C-8), 87.7 (C-6), 68.8 (C-2), 68.6 (C-4), 44.4 (C-3), 39.6 (C-1), 25.7 (C-11a), 24.5 (C-11b), 18.6 (C-15/17), 18.2 (C-15/17), 12.4 (C-14/16), 11.3 (C-14/16), 10.3 (C-13); *Minor diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.32 (s, 1H, H-8), 4.75 (d, $\mathcal{J}$ = 5.0 Hz, 1H, H-4), 3.98–3.90 (m, 1H, H-2), 2.64–2.55 (m, 2H, H-1a,12), 2.31 (dd, $\mathcal{J}$ = 14.6, 9.9 Hz, 1H, H-1b), 1.90 (app. sx, $\mathcal{J}$ = 6.7 Hz, 1H, H-3), 1.66 (app. s, 6H, H-11 [obscured]), 1.25–0.93 (m, 45H, H-13,14,15,16,17 [obscured]); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.7 (C-7), 161.1 (C-9), 107.2 (C-5), 106.6 (C-10), 95.5 (C-8), 87.1 (C-6), 71.1 (C-2), 66.0 (C-4), 46.3 (C-3), 39.5 (C-1), 25.7 (C-11a), 24.5 (C-11b), 18.6 (C-15/17), 18.2 (C-15/17), 12.4 (C-14/16), 11.8 (C-13), 11.3 (C-14/16); HRMS-ESI (*m/z*) found $[M+Na]^+$ 589.3712, $C_{31}H_{58}O_5Si_2Na$ requires 589.3715; $[\alpha]_D^{25}$ = +31.5 ^{o} (c = 1.0, $CHCl_3$).

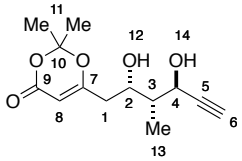
6-((2S,3R,4R)-2,4-dihydroxy-3-methyl-6-(triisopropylsilyl)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **573**



Tetrabutylammonium fluoride trihydrate (45.9 mg, 0.16 mmol) was added in one portion at 0 °C to a stirred solution of *6-((2S,3R,4R)-2-hydroxy-3-methyl-6-(triisopropylsilyl)-4-((triisopropylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **571** (6:1 *d.r.*, 38.0 mg, 0.67 mmol) in tetrahydrofuran (0.7 mL). The resulting pink solution was stirred for two hours before diluting with diethyl ether (2 mL) and quenching with the addition of sat. aq. NaCl solution (1 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 x 2 mL). The combined organic layers were passed through a plug of anhydrous $MgSO_4$ and concentrated under a steam of nitrogen gas. The resulting residues were purified by silica column chromatography, eluting in a gradient of 20–30% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a colourless oil (12.2 mg, 30 μmol, 45%).

R_F 0.24 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3446 (br., O–H), 2943, 2889, 2866, 1713 (C=O), 1634 (C=C), 1463, 1392, 1378, 1277, 1205, 1016; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.35 (s, 1H, H-8), 4.54–4.48 (m, 1H, H-2), 4.46 (app. t, $\mathcal{J}$ = 4.9 Hz, 1H, H-4), 2.66 (d, $\mathcal{J}$ = 3.9 Hz, 1H, H-12/14), 2.51–2.43 (m, 2H, H-1a,12/14), 2.30 (dd, $\mathcal{J}$ = 14.4, 3.7 Hz, 1H, H-1b), 1.84 (qdd, $\mathcal{J}$ = 7.2, 5.2, 1.9 Hz, 1H, H-3), 1.69 (s, 6H, H-11), 1.09 (d, $\mathcal{J}$ = 7.2 Hz, 3H, H-13), 1.08–1.04 (m, 21H, H-15,16); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.3 (C-7), 161.2 (C-9), 107.3 (C-5), 106.8 (C-10), 95.3 (C-8), 87.9 (C-6), 69.0 (C-2), 66.8 (C-4), 43.5 (C-3), 39.3 (C-1), 25.6 (C-11a), 24.8 (C-11b), 18.7 (C-16), 11.2 (C-15), 10.2 (C-13); HRMS-ESI (*m/z*) found $[M+H]^+$ 433.2383, $C_{22}H_{38}O_5SiNa$ requires 433.2381; $[\alpha]^{25}_D$ = +3.4 ° (c = 0.5, $CHCl_3$).

6-((2S,3R,4R)-2,4-dihydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **572**

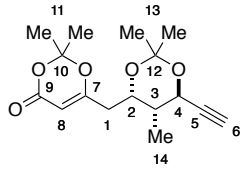


Trifluorocaetic acid (0.20 mL, 2.6 mmol) was added at 0 °C to a solution of *2,2-dimethyl-6-((2S,3R,4R)-3-methyl-2,4-bis((triethylsilyl)oxy)hex-5-yn-1-yl)-4H-1,3-dioxin-4-one* **547** (289 mg, 600 μmol) in acetonitrile (1.6 mL) and water (0.2 mL). The resulting solution was warmed to room temperature and then stirred for a further 20 minutes before quenching with the addition of sat. aq. $NaHCO_3$ solution (5 mL). The resulting mixture was extracted with dichloromethane (5 x 5 mL) with the organic extracts combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica column

chromatography, eluting with 50% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a white crystalline solid (137.9 mg, 0.54 mmol, 90%).

R_F 0.14 (50% EtOAc in pet. ether 40–60); T_m 118–120 °C; IR ν_{max}/cm^{-1} (film): 3404 (br., O–H), 3292 (*sp* C–H), 2977, 2941, 1703 (C=O), 1630 (C=C), 1461, 1392, 1376, 1276, 1202, 1086, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.36 (s, 1H, H-8), 4.50 (app. dtd, $\mathcal{J}$ = 8.9, 4.4, 2.0 Hz, 1H, H-2), 4.44 (app. td, $\mathcal{J}$ = 5.6, 2.1 Hz, 1H, H-4), 2.66 (d, $\mathcal{J}$ = 5.3, 1H, H-14), 2.58–2.55 (m, 2H, H-6,12), 2.48 (dd, $\mathcal{J}$ = 14.6, 8.9 Hz, 1H, H-1a), 2.33 (dd, $\mathcal{J}$ = 14.6, 4.1 Hz, 1H, H-1b), 1.85 (qdd, $\mathcal{J}$ = 7.1, 5.6, 2.0 Hz, 1H, H-3), 1.71 (s, 6H, H-11), 1.09 (d, $\mathcal{J}$ = 7.1 Hz, 3H, H-13); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.1 (C-7), 161.2 (C-9), 106.9 (C-10), 95.3 (C-8), 83.8 (C-5), 74.7 (C-6), 68.9 (C-2), 66.2 (C-4), 42.9 (C-3), 39.1 (C-1), 25.4 (C-11a), 25.0 (C-11b), 10.1 (C-13); HRMS-ESI (*m/z*) found $[M+Na]^+$ 277.1043, $C_{13}H_{18}O_5Na$ requires 277.1046; $[\alpha]^{25}_D$ = –8.2 ° (c = 0.5, MeCN).

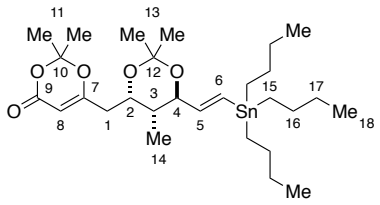
6-(((4S,5R,6R)-6-ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **574**



2,2-Dimethoxypropane (123 µL, 1.00 mmol) and camphor sulfonic acid (1.2 mg, 5.0 µmol) were added sequentially at 0 °C to a suspension of *6-((2S,3R,4R)-2,4-dihydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **572** (110.0 mg, 0.433 mmol) in dichloromethane (1.5 mL). The resulting mixture was stirred for 16 hours then quenched with the addition of sat aq. $NaHCO_3$ solution (1.5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2CO_3 and concentrated *in vacuo*. The residues were purified by silica column chromatography, eluting in a gradient of 10–20% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a white crystalline solid (111 mg, 0.378 mmol, 87%).

R_F 0.18 (20% EtOAc in pet. ether 40–60); T_m 90–92 °C; IR ν_{max}/cm^{-1} (film): 3273 (*sp* C–H), 2993, 2942, 1726 (C=O), 1637 (C=C), 1462, 1391, 1273, 1252, 1203, 1127, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.32 (s, 1H, H-8), 4.48 (app. dt, $\mathcal{J}$ = 9.5, 3.9 Hz, 1H, H-2), 4.32 (dd, $\mathcal{J}$ = 4.6, 2.4 Hz, 1H, H-4), 2.53 (d, $\mathcal{J}$ = 2.4, 1H, H-6), 2.42 (dd, $\mathcal{J}$ = 15.0, 9.5 Hz, 1H, H-1a), 2.25 (dd, $\mathcal{J}$ = 15.0, 3.9 Hz, 1H, H-1b), 1.91 (app. qt, $\mathcal{J}$ = 7.0, 4.0 Hz, 1H, H-3), 1.70 (s, 3H, H-11a), 1.69 (s, 3H, H-11b), 1.55 (s, 3H, H-13a), 1.36 (s, 3H, H-13b), 1.07 (d, $\mathcal{J}$ = 7.0 Hz, 3H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.7 (C-7), 161.1 (C-9), 106.7 (C-10), 101.3 (C-12), 95.1 (C-8), 83.6 (C-5), 74.5 (C-6), 66.5 (C-4), 65.2 (C-2), 38.6 (C-3), 36.6 (C-1), 27.9 (C-13a), 25.5 (C-11a), 25.1 (C-11b), 23.8 (C-13b), 11.7 (C-14); HRMS-ESI (*m/z*) found $[M+Na]^+$ 317.1359, $C_{16}H_{22}O_5Na$ requires 317.1359; $[\alpha]^{25}_D$ = –6.8 ° (c = 0.5, $CHCl_3$).

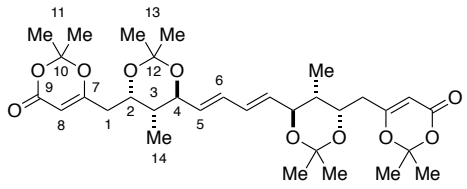
2,2-dimethyl-6-(((4S,5R,6R)-2,2,5-trimethyl-6-((E)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)methyl)-4H-1,3-dioxin-4-one **560**



Prepared according to general procedure **H** with Pd_2dba_3 (0.5 mg, 0.5 μmol) and tricylohexylphosphonium tetrafluoroborate (0.7 mg, 1.9 μmol) in dichloromethane (4 mL), di*iso*proylethylamine (0.7 μL, 1.9 μmol), *6-(((4S,5R,6R)-6-ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one* **574** (28 mg, 9.4 μmol) in dichloromethane (0.5 mL), and tributyltin hydride (32 μL, 11.9 μmol) in dichloromethane (1.5 mL). Purification was carried out by silica column chromatography, eluting in a gradient of 0 to 20% diethyl ether in petroleum ether 40–60, to furnish the title compound (containing 6% 1,1-disubstuted analogue) as a colourless oil (44 mg, 7.4 μmol, 79%).

R_F 0.35 (20% EtOAc in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 2956, 2926, 2873, 1734 (C=O), 1638 (C=C), 1462, 1387, 1378, 1271, 1227, 1205, 1163, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.15 ([d]dd, $[^2\mathcal{J}_{H-[Sn]} = 69.2$ Hz], $\mathcal{J} = 19.0$, 0.7 Hz, 1H, H-6), 5.98 ([d+d]dd, $[^3\mathcal{J}_{H-^{119}Sn} = 62.3$ Hz], $[^3\mathcal{J}_{H-^{117}Sn} = 60.9$ Hz], $\mathcal{J} = 19.0$, 6.1 Hz, 1H, H-5), 5.31 (s, 1H, H-8), 4.21 (ddd, $\mathcal{J} = 10.0$, 5.2, 3.8 Hz, 1H, H-2), 3.73 (app. t, $\mathcal{J} = 6.8$ Hz, 1H, H-4), 2.39 (dd, $\mathcal{J} = 15.0$, 10.0 Hz, 1H, H-1a), 2.26 (dd, $\mathcal{J} = 15.0$, 3.8 Hz, 1H, H-1b), 1.82 (app. tq, $\mathcal{J} = 6.9$, 6.5 Hz, 1H, H-3), 1.68 (s, 6H, H-11), 1.54–1.43 (m, 6H, H-17), 1.36 (s, 3H, H-13a), 1.35 (s, 3H, H-13b), 1.33–1.26 (m, 6H, H-16), 0.92–0.84 (m, 18H, H-14,15,18); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.3 (C-7), 161.2 (C-9), 146.7 (C-5), 130.6 ([d], $[^1\mathcal{J}_{C-[Sn]} = 364.2$ Hz], C-6), 106.5 (C-10), 101.1 (C-12), 94.8 (C-8), 79.0 (C-4), 65.8 (C-2), 39.2 (C-3), 35.9 (C-1), 29.2 ([d], $[^3\mathcal{J}_{C-[Sn]} = 20.2$ Hz],C-17), 27.4 ([d], $[^2\mathcal{J}_{C-[Sn]} = 27.4$ Hz], C-16), 25.4 (C-11a), 25.1 (2C, C-11b,13b), 24.5 (C-13a), 13.8 (C-18), 11.5 (C-14), 9.6 ([d+d], $[^1\mathcal{J}_{C-^{119}Sn} = 345.0$ Hz], $[^1\mathcal{J}_{C-^{117}Sn} = 329.6$ Hz], C-15); HRMS-SMDI (*m/z*) found [M] 586.2689, $C_{28}H_{50}O_5Sn$ requires 586.2680; $[\alpha]_D^{25} = +17.7$ ° (c = 1.0, $CHCl_3$).

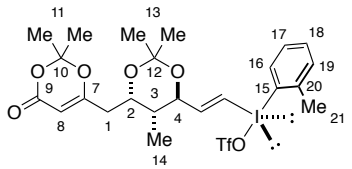
6,6'-(((4S,4'S,5R,5'R,6S,6'S)-((1E,3E)-buta-1,3-diene-1,4-diyl)bis(2,2,5-trimethyl-1,3-dioxane-6,4-diyl))bis(methylene))bis(2,2-dimethyl-4H-1,3-dioxin-4-one) **575**



Formed from *2,2-dimethyl-6-(((4S,5R,6R)-2,2,5-trimethyl-6-((E)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)methyl)-4H-1,3-dioxin-4-one* **560** on prolonged standing to give a crystalline white solid.

R_F 0.38 (50% EtOAc in pet. ether 40–60); T_m 108–110 °C; IR ν_{max}/cm^{-1} (film): 2989, 2939, 1726 (C=O), 1636 (C=C), 1460, 1387, 1378, 1272, 1226, 1204, 1164, 1014; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.24–6.15 (m, 2H, H-6), 5.76–5.65 (m, 2H, H-5), 5.28 (s, 2H, H-8), 5.22–5.15 (m, 2H, H-2), 3.78 (app. t, $\mathcal{J}$ = 7.2 Hz, 2H, H-4), 2.36 (dd, $\mathcal{J}$ = 15.0, 10.1 Hz, 2H, H-1a), 2.23 (dd, $\mathcal{J}$ = 15.0, 3.5 Hz, 2H, H-1b), 1.80 (app. sx, $\mathcal{J}$ = 6.6 Hz, 2H, H-3), 1.66 (s, 12H, H-11), 1.32 (s, 6H, H-13a), 1.31 (s, 6H, H-13b), 0.86 (d, $\mathcal{J}$ = 6.8 Hz, 6H, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.1 (C-7), 161.1 (C-9), 132.8 (C-5 [*S-cis*]) 132.6 (C-5 [*S-trams*]), 131.2 (C-6 [*S-cis*]), 130.8 (C-6 [*S-trans*]), 106.5 (C-10), 101.1 (C-12), 94.8 (C-8), 75.6 (C-4 [*S-cis*]) 75.2 (C-4 [*S-trans*]), 65.7 (C-2), 39.7 (C-3), 35.6 (C-1), 25.3 (C-11a), 25.1 (C-11b), 25.0 (C-13a), 24.2 (C-13b), 11.5 (C-14 [*S-trams*]), 11.4 (C-14 [*S-cis*]); HRMS-ESI (*m/z*) found $[M+Na]^+$ 613.2996, $C_{32}H_{46}O_{10}Na$ requires 613.2983; $[\alpha]^{25}_D$ = +25.4 ° (c = 1.0, $CHCl_3$).

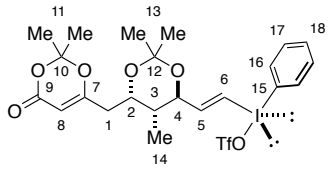
((E)-2-((4R,5R,6S)-6-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)vinyl)(o-tolyl)-iodonium trifluoromethanesulfonate **577**



Trimethylsilyl trifluoromethanesulfonate (2.0 µL, 10 µmol) was added at −78 °C too a solution of *2,2-dimethyl-6-(((4S,5R,6R)-2,2,5-trimethyl-6-((E)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)methyl)-4H-1,3-dioxin-4-one* **560** (5.9 mg, 10 µmol), [Bis(trifluoroacetoxy)iodo]*ortho*-toluene (4.4 mg, 10 µmol) and 1,3,5-trimethoxybenzene tricarboxylate (2.5 mg, 10 µmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at −78 °C for five minutes before warming to room temperature and stirring for a further five minutes. The resulting crude iodonium salt (90% assay yield) was concentrated under a stream of nitrogen gas then purified by silica column chromoatography, eluting in a gradient of 0 to 50% acetone in dichloromethane. The purified residues were precipated with diethyl ether to furnish the desired title compound as an amorphous white powder (3.1 mg, 4.5 µmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (dd, $\mathcal{J}$ = 8.1, 1.1 Hz, 1H, H-16), 7.62 (app. td, $\mathcal{J}$ = 7.5, 1.1 Hz, 1H, H-18), 7.54 (dd, $\mathcal{J}$ = 7.8, 1.3 Hz, 1H, H-19), 7.31 (app. td, $\mathcal{J}$ = 7.8, 1.3 Hz, 1H, H-17), 6.87 (dd, $\mathcal{J}$ = 13.6, 3.7 Hz, 1H, H-5), 6.81 (dd, $\mathcal{J}$ = 13.6, 1.1 Hz, 1H, H-6), 5.28 (s, 1H, H-8), 4.15 (ddd, $\mathcal{J}$ = 10.1, 5.2, 3.3 Hz, 1H, H-2), 4.02 (ddd, $\mathcal{J}$ = 8.7, 3.7, 1.1 Hz, 1H, H-4), 2.64 (s, 3H, H-21), 2.36 (dd, $\mathcal{J}$ = 14.9, 10.1 Hz, 1H, H-1a), 2.23 (dd, $\mathcal{J}$ = 14.9, 3.3 Hz, 1H, H-1b), 1.94–1.84 (m, 1H, H-3), 1.69–1.66 (m, 6H, H-11), 1.30 (s, 6H, H-13), 0.94 (d, $\mathcal{J}$ = 6.7 Hz, 3H, H-14); ^{19}F NMR (376 MHz, $CDCl_3$) *δ*: −79.2. Further characterisation data could not be obtained due to product instability.

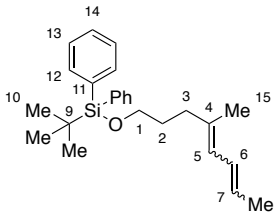
((E)-2-((4R,5R,6S)-6-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)vinyl)(phenyl)-iodonium trifluoromethanesulfonate **558**



A solution of *2,2-dimethyl-6-(((4S,5R,6R)-2,2,5-trimethyl-6-((E)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)methyl)-4H-1,3-dioxin-4-one* **560** (93% purity, 31.4 mg, 50.0 μmol) in dichloromethane (2.5 mL) was added at −40 °C to a suspension of *cyano(phenyl)iodonium trifluoromethanesulfonate* **535** (18.9 mg, 50.0 μmol) in dichloromethane (7.5 mL). The resulting suspension was warmed to room temperature and was stirred for 10 minutes then loaded directly onto a pre-packed silica column (dichloromethane) and eluted in a gradient of 0 to 100% acetone in dichloromethane. The fractions containing the iodonium salt were concentrated *in vacuo* and the resulting residues triturated with hexanes to furnish the title compound as an amorphous white powder (29.0 mg, 44.7 μmol, 89%).

R_F 0.21 (50% Me_2CO in CH_2Cl_2); IR ν_{max}/cm^{-1} (film): 3446 (br.), 2979, 2941, 1706 (C=O), 1636 (C=C), 1403, 1379, 1270, 1244, 1225, 1163, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.00 (d, $\mathcal{J}$ = 7.5 Hz, 2H, H-16), 7.66 (t, $\mathcal{J}$ = 7.3 Hz, 1H, H-18), 7.51 (app. t, $\mathcal{J}$ = 7.9 Hz, 2H, H-17), 7.03 (dd, $\mathcal{J}$ = 13.8, 4.1 Hz, 1H, H-5), 6.91 (dd, $\mathcal{J}$ = 13.8, 1.6 Hz, 1H, H-6), 5.28 (s, 1H, H-8), 4.14 (ddd, $\mathcal{J}$ = 10.2, 5.1, 3.4 Hz, 1H, H-2), 4.02 (ddd, $\mathcal{J}$ = 8.6, 4.1, 1.6 Hz, 1H, H-4), 2.35 (dd, $\mathcal{J}$ = 15.0, 10.2 Hz, 1H, H-1a), 2.23 (dd, $\mathcal{J}$ = 15.0, 3.4 Hz, 1H, H-1b), 1.91 (app. sx, $\mathcal{J}$ = 6.8, 1H, H-3), 1.67 (s, 3H, H-11a), 1.66 (s, 3H, H-11b), 1.293 (s, 3H, H-13a), 1.289 (s, 2H, H-13b), 0.94 (d, $\mathcal{J}$ = 6.9 Hz, 3H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.8 (C-7), 161.2 (C-9), 150.0 (C-5), 136.0 (C-16), 132.8 (C-18), 132.4 (C-17), 120.3 (q, $^1\mathcal{J}$ = 319.9 Hz, C-Tf), 110.6 (C-15), 106.7 (C-10), 101.8 (C-12), 99.3 (C-6), 94.9 (C-8), 75.9 (C-4), 65.6 (C-2), 38.9 (C-3), 35.4 (C-1), 25.25 (C-11a), 25.17 (C-11b), 24.7 (C-13a), 24.2 (C-13b), 11.5 (C-14); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −79.2; HRMS-ESI (*m/z*) found $[M–OTf]^+$ 499.0964, $C_{22}H_{28}O_5I$ requires 499.0976; $[\alpha]_D^{25}$ = −19.0 ° (c = 0.5, MeCN).

tert-butyl((4-methylocta-4,6-dien-1-yl)oxy)diphenylsilane **584**

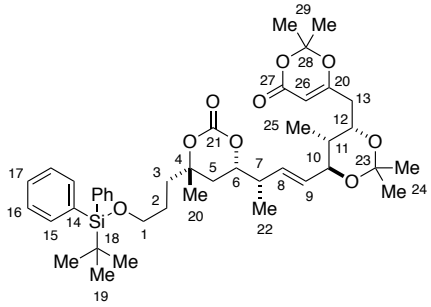


n-Butyllithium (1.9 M in hexanes, 0.87 mL, 1.65 mmol) was added at 0 °C to a solution of *but-2-en-1-yltriphenylphosphonium bromide* **588** (5:1 *E*-:*Z*-, 596 mg, 1.50 mmol) in tetrahydrofuran (10 mL). The resulting mixture was stirred for 1 hour before undergoing the dropwise addition of a solution of *5-((tert-butyldiphenylsilyl)oxy)pentan-2-one* **586** (510 mg, 1.50 mmol) in tetrahydrofuran (5 mL). The resulting

solution was warmed to room temperature and was then stirred for a further 16 hours before pouring into hexanes (50 mL). The precipiated triphenylphosphine oxide was removed by filtration, with the filtrate taken and concentrated *in vacuo*. The resulting residues were purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless viscous oil and as an inseparable complex mixture of four diastereoisomers (366 mg, 0.97 mmol, 63%).

R_F 0.09 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3071, 3026, 2956, 2931, 2857, 1473, 1428, 1187, 1107, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76–7.69 (m, 4H, H-13), 7.53–7.36 (m. 6H, H-12,14), 6.40–6.23 (m, 1H, H-6), 6.23–6.12 (m, 0.25H, H-5), 5.84 (d, $\mathcal{J}$ = 10.7 Hz, 0.75H, H-5'), 5.67–5.55 (m, 0.75H, H-7), 5.52–5.37 (m, 0.25H, H-7'), 3.71 (m, 2H, H-1), 2.33–2.27 (m, 0.8H, H-3), 2.26–2.20 (m, 0.3H, H-3'), 2.17–2.13 (m, 0.9H, H-3''), 1.86–1.65 (m, 8H, H-2,8,15), 1.13–1.08 (m, 9H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.6 (C-4), 138.2 (C-4'), 136.2 (C-4''), 135.8 (C-4'''), 135.7 (C-13), 134.2 (C-11), 129.7 (C-14), 128.2 (C-6), 128.0 (C-6'). 127.7 (C-12), 126.9 (C-7), 126.7 (C-7'), 125.8 (C-5), 125.5 (C-6''), 124.9 (C-5'), 124.0 (C-7''), 123.8 (C-7'''), 120.7 (C-5''), 120.1 (C-5'''), 63.6 (C-1), 36.6 (C-3), 36.1 (C-3'), 31.3 (C-2), 31.0 (C-2'), 28.63 (C-3''), 28.56 (C-3'''), 27.0 (C-10), 24.3 (C-15), 23.7 (C-15'), 18.5 (C-8), 18.4 (C-8'), 16.6 (C-15''), 16.5 (C-15'''), 13.3 (C-8''), 13.2 (C-8'''); HRMS-ESI (*m/z*) found $[M+H]^+$ 379.2448, $C_{25}H_{35}OSi$ requires 379.2452.

6-(((4S,5R,6S)-6-((S,E)-3-((4S,6S)-6-(3-((tert-butyldiphenylsilyl)oxy)propyl)-6-methyl-2-oxo-1,3-dioxan-4-yl)but-1-en-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **559**



A solution of *((E)-2-((4R,5R,6S)-6-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)vinyl)(phenyl)-iodonium trifluoromethanesulfonate* **558** (52.7 mg, 81.6 μmol) and *(S,E)-1-((tert-butyldiphenylsilyl)oxy)-4-methyloct-6-en-4-yl dimethylcarbamate* **470** (29.3 mg, 62.7 μmol) in dichloromethane (1 mL) was added to a sealed microwave vial charged with $(CuOTf)_2$•PhH (4.7 mg, 9.4 μmol) and 4 Å molecular sieves (29.3 mg) under an atmosphere of nitrogen. Di-*tert*-butyl pyridine (14 μL, 63 μmol) was added and the resulting reaction mixture stirred for 21 hours at room temperature. The reaction was quenched with the addition of sat. aq. $NaHCO_3$ solution (1 mL) and triethylamine (0.5 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 2 mL). The organic fractions were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residues were purified by five rounds of silica column chromatography, eluting in 0–5% ethyl acetate in

petroleum ether, then by a final round of silica column chromatography, eluting in 2% acetone in dichloromethane, to furnish the title compound as a colourless oil (1.0 mg, 1.3 μmol, 2%).

R_F 0.17 (40% EtOAc in pet. ether 40–60); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.66–7.62 (m, 4H, H-16), 7.46–7.35 (m, 6H, H-15,17), 5.74–5.56 (m, 2H, H-8,9), 5.32 (s, 1H, H-26), 4.42–4.18 (m, H-6,12), 3.78–3.62 (m, 3H, H-1,10), 2.52–2.33 (m, 2H, H-7,13a), 2.28–2.21 (m, 1H, H-13b), 1.69 (s, 6H, H-29), 1.36–1.34 (m, 6H, H-24), 1.06–1.03 (m, 9H, H-19), H-2,3,5,11,22,25 indistinguishable; HRMS-ESI (*m/z*) found $[M+Na]^+$ 757.3728, $C_{42}H_{58}O_9SiNa$ requires 757.3742. Further characterisation data could not be obtained due to limited product availability.

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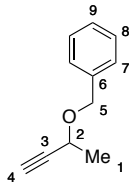
vii Appendix 1 – Synthesis of Supporting Compounds

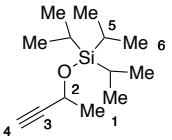
((but-3-yn-2-yloxy)methyl)benzene **539**[195]



Adapted from a procedure reported by Nakai et al.[197] Benzyl bromide (7.72 mL, 65.0 mmol) was added dropwise at 0 °C to a vigorously stirred mixture of but-3-yn-2-ol (3.91 mL, 50.0 mmol), tetrabutylammonium iodide (920 mg, 2.50 mmol), NaOH (8.00 g, 200 mmol) and water (2.5 mL). The resulting reaction mixture was warmed to room temperature and was stirred for 16 hours before being quenched with sat. aq. NH_4Cl solution (50 mL). The layers were separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by alumina column chromatography, eluting with 0 to 1% diethyl ether in petroleum ether 40–60, to give the title compound as colourless oil (3.65 g, 22.8 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43–7.28 (m, 5H, H-7,8,9), 4.82 (d, $\mathcal{J}$ = 11.7 Hz, 1H, H-5a), 4.53 (d, $\mathcal{J}$ = 11.7 Hz, 1H, H-5b), 4.24 (qd, $\mathcal{J}$ = 6.7, 2.0 Hz, 1H, H-2), 2.49 (d, $\mathcal{J}$ = 2.0 Hz, 1H, H-4), 1.51 (d, $\mathcal{J}$ = 6.7 Hz, 3H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.9 (C-6), 128.5 (C-8), 128.1 (C-7), 127.8 (C-9), 83.8 (C-3), 73.3 (C-4), 70.6 (C-5), 64.3 (C-2), 22.1 (C-1). Experimental data in agreement with previous literature report.[195]

(but-3-yn-2-yloxy)triisopropylsilane **483a**

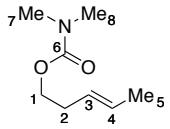


Triisopropylsilyl trifluoromethanesulfonate (2.78 mL, 15.2 mmol) was added dropwise at 0 °C to a solution of but-3-yn-2-ol (1.00 mL, 12.7 mmol) and 2,6-lutidine (2.89 mL, 25.4 mmol) in dichloromethane (30 mL). The resulting solution was warmed to room temperature and was stirred for a further three hours before quenching with sat. aq. $NaHCO_3$ solution (30 mL). The biphasic mixture was separated and the aqueous layer extracted with dichloromethane (3 x 30 mL). The organic layers were combined, washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (1.90 g, 8.40 mmol, 66%).

R_F 0.72 (2% Et_2O in pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3313 (*sp* C–H), 2944, 2866, 1464, 1250, 1121, 1101, 1059, 974, 882; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.60 (qd, $\mathcal{J}$ = 6.5, 2.0 Hz, 1H, H-2),

2.37 (d, $\mathcal{J}$ = 2.0 Hz, 1H, H-4), 1.46 (d, $\mathcal{J}$ = 6.5 Hz, 3H, H-1), 1.17–1.03 (m, 21H, H-5,6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 86.8 (C-3), 71.2 (C-4), 58.9 (C-2), 25.7 (C-1), 18.1 (C-6), 12.3 (C-5). HRMS-ESI (*m/z*) found M^+ 266.1754, $C_{13}H_{26}OSi$ requires 266.1754.

(E)-pent-3-en-1-yl dimethylcarbamate **317**[158]



Prepared according to a procedure adapted from Gaunt et al.[158] Sodium metal (1.00 g, 43.5 mmol) was dissolved in liquid ammonia (50 mL, condensed into a Schlenk flask held at −78 °C). A solution of 3-pentyn-1-ol (1.14 mL, 12.4 mmol) in dry diethyl ether (6 mL) was added dropwise to the resulting bright blue solution with this mixture stirred for a further four hours. The reaction was then opened to the atmosphere, solid ammonium chloride (1.19 g, 22.2 mmol) added in one portion, and the resulting mixture warmed to room temperature. Following evaporation of the ammonia, ice/water (150 mL) was added to the residue and mixture then extracted with diethyl ether (5 x 10 mL). The combined organic layers were then washed with water (10 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* (maintaining rotary evaporator bath at 0 °C) to furnish the intermediate *trans*-3-penten-1-ol as a solution in diethyl ether (1.06 g, 40 wt%, 4.90 mmol, 40%).

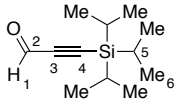
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.66–5.54 (m, 1H, H-4), 5.46–5.34 (m, 1H, H-3), 3.63 (app. q, $\mathcal{J}$ = 5.5 Hz, 2H, H-1), 2.26 (app. q, $\mathcal{J}$ = 6.5 Hz, 2H, H-2), 1.69 (app. dq, $\mathcal{J}$ = 6.4, 0.9 Hz, 3H, H-5). Experimental data in agreement with previous literature report.[224]

To a solution of *trans*-3-penten-1-ol (1.06 g, 40 wt% in Et_2O, 4.90 mmol) in acetonitrile (10 mL) was added carbonyldiimidazole (3.00 g, 18.5 mmol) portion-wise against a counter-flow of nitrogen gas. The resulting solution was heated to 35 °C for 30 minutes before re-cooling to room temperature. Dimethylamine (2.0 M in THF, 9.4 mL, 18.8 mmol) was added to the yellow solution with the reaction mixture then warmed to 30 °C for a further 45 minutes. The resulting solution was concentrated *in vacuo* and the residue re-suspended in 1M aqueous HCl (10 mL) and dichloromethane (10 mL). The layers were separated and the aqueous extracted with further quantities of dichloromethane (3 x 10 mL). The organic fractions were combined, dried over anhydrous $MgSO_4$, concentrated *in vacuo.* The resulting residue was purified by silica column chromatography, eluting in a gradient of 2.5–5% ethyl acetate in petroleum ether 40–60. The purified homoallylic carbamate was then further purified by kugelrohr distillation to furnish the title compound as a colourless oil (584 mg, 3.72 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.58–5.48 (m, 1H, H-4), 5.46–5.36 (m, 1H, H-3), 4.05 (t, $\mathcal{J}$ = 6.8 Hz, 2H, H-1), 2.89 (br. s, 6H, H-7,8), 2.30 (app. qt, $\mathcal{J}$ = 6.8, 1.1 Hz, 2H, H-2), 1.66 (app. dq, $\mathcal{J}$ = 6.3, 1.1 Hz, 3H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.8 (C-6), 127.7 (C-4), 126.8 (C-3), 65.1 (C-

1), 36.4 (C-7/8), 35.9 (C-7/8), 32.6 (C-2), 18.1 (C-5). Experimental data in agreement with previous literature report.[158]

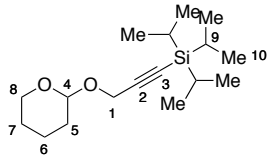
3-(triisopropylsilyl)prop-2-yn-1-o 3-(triisopropylsilyl)propiolaldehyde **494**[225]



Adapted from a procedure reported by Aponick et al.[225] *n*-Butyllithum (1.8 mL, 2.5 M, 4.5 mmol) was added dropwise at −78 °C to a stirred solution of tri*iso*propylsilylacetylene (1.0 mL, 4.5 mmol) in tetrahydrofuran (12.5 mL). The resulting mixture was stirred at 0 °C for 30 minutes before it was warmed to room temperature, stirred for ten minutes then cooled to −78 °C. Dimethylformamide (0.70 mL, 9.0 mmol) was added dropwise to the cold mixture and the reaction was stirred at −78 °C for 10 minutes before warming to room temperature and stirring for a further 30 minutes. The reaction was quenched by pouring into a 0 °C mixture of 10% aqueous NaH_2PO_4 (50 mL) and diethyl ether (50 mL) and was stirred for five minutes. The layers were separated and the organic phase was washed with water (25 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residues were purified by silica column chromatography, eluting in a gradient of 1 to 2% diethyl ether in petroleum ether 40–60, to furnish the title compound as a colourless oil (0.876 g, 4.16 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H, H-1), 1.14–1.06 (m, 21H, H-5,6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.9 (C-2), 104.6 (C-4), 101.2 (C-3), 18.5 (C-5), 11.1 (C-6). Experimental data in agreement with previous literature report.[225]

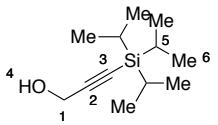
triisopropyl(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)silane **510a**[226]



Prepared according to a procedure reported by Barriault et al.[227] *n*-BuLi (8.40 mL, 2.5 M, 21.0 mmol) was added dropwise at −40 °C to a stirred solution of THP-protected proparyl alcohol (2.80 mL, 20.0 mmol) in tetrahydrofuran (10 mL). The resulting solution was maintained at this temperature for two hours before being cooled to −78 °C and undergoing a dropwise addition of triisopropylsilyl chloride (5.10 mL, 24.0 mmol). The resulting orange suspension was maintained at −78 °C for a further hour before warming to room temperature and stirring for a further three hours. The reaction mixture was then quenched with sat. aq. NH_4Cl solution (20 mL), separated, and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude orange oil was purified by silica column chromatography, eluting with 0–10% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a yellow oil (4.73 g, 15.9 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.90 (app. t, $\mathcal{J}$ = 3.4 Hz, 1H, H-4), 4.33 (d, $\mathcal{J}$ = 16.1 Hz, 1H, H-1a), 4.27 (d, $\mathcal{J}$ = 16.1 Hz, 1H, H-1b), 3.86 (ddd, $\mathcal{J}$ = 11.3, 8.5, 2.8 Hz, 1H, H-8_{ax}), 3.57–3.46 (m, 1H, H-8_{eq}), 1.90–1.68 (m, 2H, H-5_{ax},6_{ax}), 1.66–1.48 (m, 4H, H-5_{eq},6_{eq},7), 1.09–1.05 (m, 21H, H-9,10); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 103.5 (C-2), 96.4 (C-4), 87.2 (C-3), 62.3 (C-8), 54.8 (C-1), 30.5 (C-5), 25.6 (C-7), 19.3 (C-6), 18.7 (C-10), 11.3 (C-9). Experimental data in agreement with previous literature report.[226]

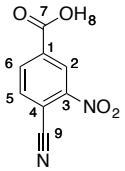
3-(triisopropylsilyl)prop-2-yn-1-ol **510**[228]



Adapted from a procedure reported by Barriault et al.[227] *Para*-toluenesulfonic acid (215 µL, 12 wt% in AcOH, 0.15 mmol) was added to *triisopropyl(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)silane* **510a** (4.44 g, 15.0 mmol) in methanol (15 mL) and the mixture heated at reflux for 17 hours. The resulting solution was allowed to cool to room temperature and was concentrated *in vacuo*. The resulting residue was then re-dissolved in a biphasic mixture of ethyl acetate (20 mL) and water (20 mL). The mixture was separated and the aqueous layer extracted with further portions of ethyl acetate (2 x 20 mL). The organics layers were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue (3:2 desired product to starting material), was purified by silica column chromatography, eluting with a gradient of 2–10% ethyl acetate in petroleum ether 40–60, to furnish the title compound as a pale yellow oil (1.32 g, 6.20 mmol, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.29 (s, 2H, H-1), 1.69 (br. s, 1H, H-4), 1.09–1.05 (m, 21H, H-5,6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 105.8 (C-2), 86.9 (C-3), 51.9 (C-1), 18.7 (C-6), 11.3 (C-5). Experimental data in agreement with previous literature report.[228]

4-cyano-3-nitrobenzoic acid

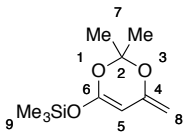


Adapted from a procedure reported by Zambach et al.[229] Periodic acid (4.92 g, 21.7 mmol) was suspended in acetonitrile (77 mL) under an atmosphere of argon gas and the resulting mixture vigorously stirred for fifteen minutes. Chromium (VI) oxide (250 mg, 25.0 mmol) and 4-methyl-2-nitrobenzonitrile (1.00 g, 6.21 mmol) were then added and the resulting orange solution was stirred for 16 hours at room temperature before the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and extracted with aqueous 1M Na_2CO_3 solution (3 x 25 mL). The combined aqueous layers were acidified with 3M HCl and then back extracted with

dichloromethane (3 x 50 mL). The organic fractions were combined, washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting pale yellow solid was purified by silica column chromatography, flushing with 5% methanol in dichloromethane then eluting with a mixture of 1% acetic acid in 5% methanol in dichloromethane to give the title compound as an off-white crystalline solid (819 mg, 4.26 mmol, 69%).

T_m 182–184 °C; IR ν_{max}/cm^{-1} (film): 3108 (br., O–H), 2254 (C≡N), 1740 (C=O), 1727 (C=O), 1622, 1564, 1542 (NO_2 symm.), 1495, 1395, 1342 (NO_2 antisymm.), 1231, 1221, 1116; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 8.66 (d, $\mathcal{J}$ = 1.5 Hz, 1H, H-2), 8.40 (dd, $\mathcal{J}$ = 7.9, 1.5 Hz, 1H, H-6), 8.29 (d, $\mathcal{J}$ = 7.9 Hz, 1H, H-5); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm): 164.6 (C-4), 148.6 (C-3), 136.5 (C-5), 136.0 (C-1), 134.7 (C-6), 125.6 (C-2), 115.2 (C-9), 110.3 (C-7); HRMS-ESI (*m/z*) found $[M\text{-}H]^-$ 191.0100, $C_8H_3N_2O_4$ requires 191.0098.

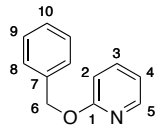
((2,2-dimethyl-4-methylene-4H-1,3-dioxin-6-yl)oxy)trimethylsilane **459**[230]



Adapted from a procedure reported by Gademann et al.[199] *n*-BuLi (48.7 mL, 2.5 M in hexanes, 122 mmol) was added dropwise over ten minutes at 0 °C to a stirred solution of freshly-distilled di*iso*propylamine (17.1 mL, 122 mmol) in anhydrous tetrahydrofuran (62 mL). The resulting colourless solution was stirred 0 °C for a further 20 minutes before being cooled to −78 °C and undergoing the dropwise addition of freshly distilled 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (13.3 mL, 100 mmol). The resulting yellow solution was stirred at −78 °C for a further hour before undergoing the dropwise addition of trimethylsilyl chloride (18.1 mL, 142 mmol). The orange suspension was warmed to room temperature over 90 minutes, filtered under a nitrogen atmosphere, and the clear filtrate concentrated *in vacuo*. The resulting orange residue was distilled under reduced pressure (care: substantial product decomposition is observed with heating over 50 °C) to give the title compound as a colourless oil (17.1 g, 79.8 mmol, 80%).

T_b 44–46 °C (0.515 mbar); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.64 (s, 1H, H-5), 4.06 (s, 1H, H-8a), 3.87 (s, 1H, H-8b), 1.54 (s, 6H, H-7), 0.26 (s, 9H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.5 (C-6), 151.9 (C-4), 102.6 (C-2), 85.1 (C-8), 76.7 (C-5), 24.6 (C-7), 0.4 (C-9). Experimental data in agreement with previous literature report.[230]

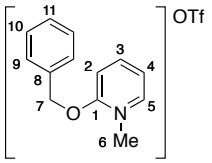
2-(benzyloxy)pyridine **522a**



Prepared according to a procedure reported by Dudley et al.[201] A suspension of benzyl alcohol (1.92 mL, 18.5 mmol), 2-chloropyridine (2.88 mL, 30.5 mmol), potassium hydroxide (3.42 g, 61.0 mmol), and 18-crown-6 (25.0 mg, 0.9 mmol) in toluene (37 mL) was heated to reflux for one hour with the azeotropic removal of water. The resulting reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), washed successively with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica column chromatography, eluting with 1% ethyl acetate in petroleum ether 40–60, to give the title compound as a colourless oil (3.21 g, 17.3 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.18 (dd, $\mathcal{J}$ = 5.1, 1.8 Hz, H-5), 7.59 (ddd, $\mathcal{J}$ = 8.3, 7.1, 1.8 Hz, H-3), 7.50–7.44 (m, 2H, H-8), 7.41–7.35 (m, 2H, H-9), 7.34–7.29 (m, 1H, H-10), 6.89 (ddd, $\mathcal{J}$ = 7.1, 5.1, 0.5 Hz, H-4), 6.81 (d, 8.3 Hz, H-2), 5.39 (s, 2H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.8 (C-1), 147.0 (C-5), 138.7 (C-3), 137.5 (C-7), 128.6 (C-9), 128.1 (C-8), 127.9 (C-10), 117.0 (C-4), 111.5 (C-2), 67.6 (C-6). Experimental data in agreement with previous literature report.[231]

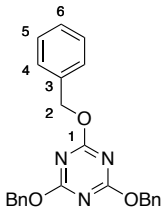
2-(benzyloxy)-1-methylpyridinium trifluoromethanesulfonate **522**



Prepared according to a procedure reported by Dudley et al.[201] Methyl trifluoromethanesulfonate (0.64 mL, 5.7 mmol) was added dropwise at 0 °C to a solution of *2-(benzyloxy)pyridine* **X** (1.00 g, 5.4 mmol) in toluene (5.4 mL). The reaction mixture was warmed to room temperature and was stirred for 40 minutes to result in product precipitation. The precipitate was collected by filtration and dried *in vacuo* to give the title compound as a colourless amorphous solid (1.85 g, 5.3 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (dd, $\mathcal{J}$ = 6.5, 1.5 Hz, H-5), 8.29 (ddd, $\mathcal{J}$ = 9.0, 7.4, 1.5 Hz, H-3), 7.65 (d, $\mathcal{J}$ = 9.0 Hz, H-2) 7.50–7.43 (m, 2H, H-9), 7.42–7.31 (m, 4H, H-4,10,11), 5.51 (s, 2H, H-7), 4.01 (s, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.6 (C-1), 148.2 (C-5), 143.9 (C-3), 132.6 (C-8), 129.7 (C-11), 128.1 (C-9), 127.9 (C-10), 119.4 (C-4), 112.2 (C-2), 74.6 (C-6), 42.0 (C-6). Experimental data in agreement with previous literature report.[201]

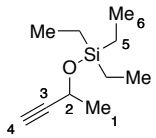
2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT) **523**



Prepared according to a procedure reported by Kunishima et al.[202] Powdered sodium hydroxide (668 mg, 16.5 mmol) was added at room temperature to neat benzyl alcohol (4.70 mL, 45.0 mmol) and the resulting suspension cooled to 0 °C. Cyanuric chloride (920 mg, 5.0 mmol) was added portion-wise to the cooled reaction mixture and the resulting mixture stirred for 30 minutes then heated to 50 °C for a further two hours. The reaction mixture was then cooled to room temperature and passed through a plug of silica gel, eluting with diethyl ether. The crude residue was concentrated and the residual benzyl alcohol removed with heating *in vacuo*. The resulting white solid was purified by silica column chromatography, eluting with 1% methanol in dichloromethane, to give the title compound as a colourless amorphous solid (1.33 g, 3.33 mmol, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49–7.43 (m, 6H, H-5), 7.42–7.30 (m, 9H, H-6,4), 5.47 (s, 6H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.1 (C-1), 135.4 (C-3), 128.6 (C-5), 128.5 (C-6), 128.4 (C-4), 70.0 (C-2). Experimental data in agreement with previous literature report.[202]

(but-3-yn-2-yloxy)triethylsilane **532**

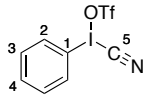


Triethylsilyl trifluoromethanesulfonate (2.26 mL, 10.0 mmol) was added dropwise at −78 °C to a stirred solution of but-3-yn-2-ol (787 µL, 10.0 mmol) and 2,6-lutidine (2.33 mL, 20.0 mmol) in dichloromethane (50 mL). The resulting suspension was warmed to room temperature and stirred twelve hours. The reaction mixture was quenched on the addition of sat. aq. $NaHCO_3$ solution (50 mL) and the resulting biphasic mixture was separated and the aqueous layer extracted with further portions of dichloromethane (3 x 25 mL). The organic fractions were combined, washed with brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica column chromatography, eluting in 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (1.02 g, 5.54 mmol, 55%).

R_F 0.26 (100% pet. ether 40–60); IR ν_{max}/cm^{-1} (film): 3313 (*sp* C–H), 2956, 2878, 1459, 1415, 1370, 1315, 1239, 1120, 1101, 1005, 971; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.51 (dq, $\mathcal{J}$ = 6.5, 2.0 Hz, 1H, H-2), 2.36 (d, $\mathcal{J}$ = 2.0 Hz, 1H, H-4), 1.43 (d, $\mathcal{J}$ = 6.5 Hz, 3H, H-1), 0.97 (t, $\mathcal{J}$ = 7.7 Hz, 9H, H-6), 0.65 (q, $\mathcal{J}$ = 7.7 Hz, 6H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 86.5 (C-3), 71.3 (C-4), 58.6 (C-2),

25.6 (C-1), 6.9 (C-6), 4.8 (C-5); HRMS-APCI (*m/z*) found $[M–Et]^+$ 155.0894, $C_8H_{15}OSi$ requires 155.0892.

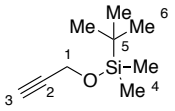
cyano(phenyl)iodonium trifluoromethanesulfonate **535**[158]



Prepared according to a procedure reported by Holt et al.[158] Trimethylsilyltrifluoromethanesulfonate (1.80 mL, 9.90 mmol) was added to a stirred solution of bis(trifluoroacetoxy)iodobenzene (4.0 g, 9.00 mmol) in dichloromethane (18 mL) held at −20 °C. The mixture was warmed to room temperature over 20 minutes, with the colour changing from colourless to a vivid yellow. The reaction mixture was re-cooled to −30 °C and trimethylsilylcyanide (1.30 mL, 9.90 mmol) was added dropwise. The resulting suspension was warmed to room temperature and filtered. The precipitate was washed with cold diethyl ether (80 mL) and collected to furnish the title compound as an off-white solid (3.17 g, 8.30 mmol, 93%).

^{1}H NMR (400 MHz, d_3-MeCN) δ (ppm): 8.34 (d, $\mathcal{J}$ = 8.0 Hz, 2H, H-2), 7.85 (t, $\mathcal{J}$ = 7.4, 1H, H-4), 7.69 (app. t, $\mathcal{J}$ = 7.9); ^{13}C NMR (100 MHz, d_3-MeCN) δ (ppm): 136.7 (C-2), 135.2 (C-4), 134.2 (C-3), 120.9 (q, $^1\mathcal{J}$ = 318.9 Hz, C-Tf), 119.1 (C-1), 68.8 (C-5). Experimental data in agreement with previous literature report.[158]

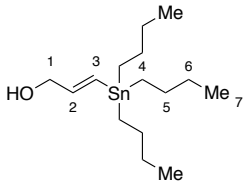
tert-butyldimethyl(prop-2-yn-1-yloxy)silane **561a**[232]



Prepared according to a procedure reported by Sakaguchi and Ohfune et al.[232] (*Tert*-butyl)dimethylsilyl chloride (4.00 g, 26.8 mmol) was added in one portion at 0 °C to a solution of propargyl alcohol (1.00 g, 17.8 mmol) and imidazole (1.80 g, 26.8 mmol) in dichloromethane (50 mL). The resulting suspension was warmed to room temperature and stirred for a further two hours before being quenched by the addition of sat. aq. NH_4Cl solution. The phases were separated and the aqueous layer was extracted with further portions of dichloromethane (2 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residues were purified by silica column chromatography, eluting with 100% petroleum ether 40–60, to furnish the title compound as a colourless oil (1.72 g, 10.0 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.31 (d, $\mathcal{J}$ = 2.4 Hz, 2H, H-1), 2.38 (t, $\mathcal{J}$ = 2.4 Hz, 1H, H-3), 0.91 (s, 9H, H-6), 0.12 (s, 6H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 82.6 (C-2), 73.0 (C-3), 51.7 (C-1), 25.9 (C-6), 18.4 (C-5), −5.1 (C-4). Experimental data in agreement with previous literature report.[232]

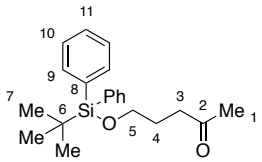
(E)-3-(tributylstannyl)prop-2-en-1-ol **561**[233]



Prepared according to a procedure reported by Menche et al.[233] A flask was charged with *tert-butyldimethyl(prop-2-yn-1-yloxy)silane* **561a** (1.53 g, 8.96 mmol), tributyltin hydride (2.90 mL, 10.7 mmol) and azobis*iso*butyronitrile (44.3 mg, 0.27 mmol), evacuated and back-filled with nitrogen. The resulting mixture was heated at 80 °C for two hours before being cooled to room temperature and diluted with tetrahydrofuran (18 mL). The crude stannylated solution was cooled to 0 °C then underwent the addition of tetrabutylammonium fluoride solution (18 mL, 1.0 M in THF, 18.0 mmol). The resulting orange mixture was warmed to room temperature and stirred for a further two hours before being quenched by the addition of sat. aq. NH_4Cl solution (25 mL). The phases were then separated and the aqueous layer extracted with diethyl ether (2 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residues were purified by silica column chromatography, eluting in a gradient of 5–10% diethyl ether in petroleum ether 40–60, to furnish the title product as a colourless oil (395 mg, 1.14 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.29 (m, 2H, H-2,3), 4.17 (dd, $\mathcal{J}$ = 6.0, 3.5 Hz. 2H, H-1), 1.57–1.40 (m, 7H, H-5,O–H), 1.30 (app. sx, $\mathcal{J}$ = 7.3 Hz, 6H, H-6), 0.92–0.86 (m, 15H, H-4,7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.2 (C-2), 128.5 ([d+d], [$^1\mathcal{J}_{C-^{119}Sn}$ = 372.8 Hz], [$^1\mathcal{J}_{C-^{117}Sn}$ = 355.9 Hz], C-3), 66.5 ([d+d], [$^2\mathcal{J}_{C-^{119}Sn}$ = 65.9 Hz], [$^2\mathcal{J}_{C-^{117}Sn}$ = 62.9 Hz], C-1), 29.2 ([d], [$^3\mathcal{J}_{C-[Sn]}$ = 20.4 Hz], C-6), 27.4 ([d+d], [$^2\mathcal{J}_{C-^{119}Sn}$ = 55.9 Hz], [$^2\mathcal{J}_{C-^{117}Sn}$ = 53.8 Hz], C-5), 13.8 (C-7), 9.6 ([d+d], [$^1\mathcal{J}_{C-^{119}Sn}$ = 345.1 Hz], [$^1\mathcal{J}_{C-^{117}Sn}$ = 329.9 Hz], C-4). Experimental data in agreement with previous literature report.[233]

5-((tert-butyldiphenylsilyl)oxy)pentan-2-one **586**[234]

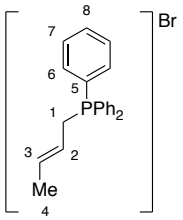


Tert-butyl(chloro)diphenyl silane (1.43 mL, 5.50 mmol) was added dropwise at 0 °C to a stirred suspension of 5-hydroxypentan-2-one (506 µL, 5.00 mmol), imidazole (680 mg, 10.0 mmol) and 4-dimethylaminopyridine (61.1 mg, 0.50 mmol) in dichloromethane (25 mL). The resulting suspension was warmed to room temperature and stirred for 24 hours before quenching with sat. aq. NH_4Cl solution (25 mL). The phases were separated and the aqueous layer extracted with dichloromethane (2 x 15 mL). The combined organic fractions were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residues were purified by silica column

chromatography, eluting in a gradient of 3 to 5% ethyl acetate in petroleum ether 40–60, and then by kugelrohr distillation to furnish the title compound as a colourless oil (566 mg, 1.66 mmol, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68–7.64 (m, 4H, H-10), 7.45–7.36 (m, 6H, H-9,11), 3.67 (t, J = 6.1 Hz, 2H, H-5), 2.55 (t, J = 7.3 Hz, 2H, H-3), 2.13 (s, 3H, H-1), 1.83 (app. qn, J = 6.7 Hz, 2H, H-4), 1.06 (s, 9H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.1 (C-2), 135.7 (C-10), 133.9 (C-8), 129.8 (C-11), 127.8 (C-9), 63.1 (C-5), 40.3 (C-3), 30.1 (C-1), 27.0 (C-7), 26.8 (C-1), 19.4 (C-6). Experimental data in agreement with previous literature report.[234]

(E)-but-2-en-1-yltriphenylphosphonium bromide **588**[235]



Prepared according to a procedure reported by Orfanopoulos et al.[235] A microwave tube was charged with crotyl bromide (6:1 *E*- to *Z*-, 400 µL, 3.80 mmol) and triphenylphosphine (1.02 g, 3.80 mmol), sealed, flushed with nitrogen and then heated at 80 °C for 12 hours. The resulting white solid was collected by filtration and washed with hot toluene to furnish the title compound as a white powder in a 5:1 *E*- to *Z*-diasteroisomeric mixture (1.30 g, 3.27 mmol, 84%).

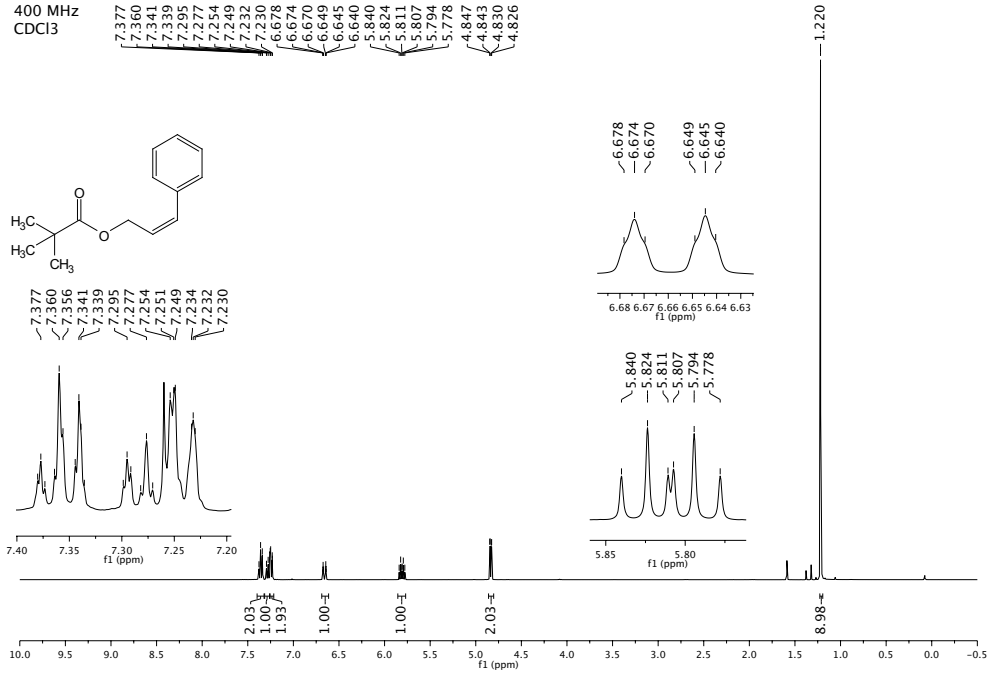
E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79–7.72 (m, 9H, H-6,8), 7.67–7.60 (m, 6H, H-7), 5.97–5.85 (m, 1H, H-2), 5.29–5.18 (m, 1H, H-3), 4.59 (dd, J_{P-H} = 14.5 Hz, J = 7.2 Hz, 2H, H-1), 1.56 (app. t, J = 5.9 Hz, 3H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.8 (d, J = 13.5 Hz, C-2), 135.0 (d, J = 3.0 Hz, C-8), 133.9 (d, J = 9.7 Hz, C-6), 130.3 (d, J_{P-C} = 12.5 Hz, C-7), 118.1 (d, J_{P-C} = 85.7 Hz, C-5), 114.8 (d, J_{P-C} = 9.8 Hz, C-3), 27.9 (d, J_{P-C} = 49.5, C-1), 18.4 (d, J_{P-C} = 2.6 Hz, C-4); *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85–7.71 (m, 9H, H-6,8), 7.67–7.60 (m, 6H, H-7), 5.85–5.75 (m, 1H, H-2), 5.41–5.30 (m, 1H, H-3), 4.56 (dd, J_{H-P} = 14.5 Hz, J = 8.0 Hz, 2H, H-1), 1.32 (app. t, J = 6.6 Hz, 3H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.1 (2C, C-2,8), 133.9 (d, J_{P-C} = 9.7 Hz, C-6), 130.4 (d, J_{P-C} = 12.6 Hz, C-7), 118.1 (d, J_{P-C} = 85.7 Hz, C-5), 114.6 (d, J_{P-C} = 9.1 Hz, C-3), 23.6 (d, J_{P-C} = 50.3, C-1), 13.7 (d, J_{P-C} = 3.0 Hz, C-4). Experimental data in agreement with previous literature report.[235]

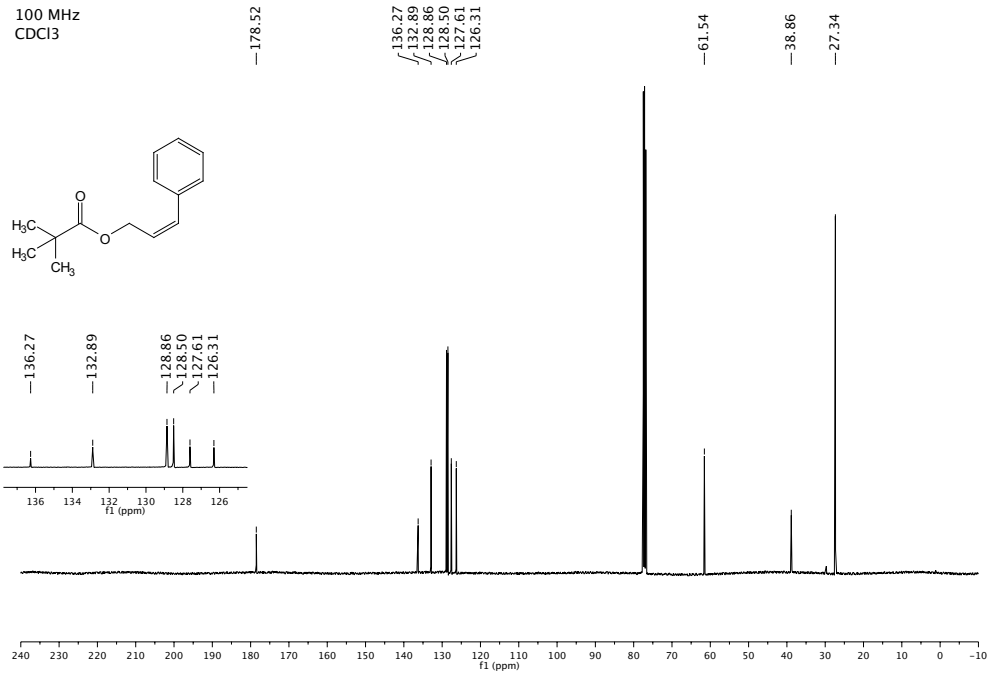
viii Appendix 2 – NMR Spectra

viii.1 The Enantioselective and Regiodivergent Copper-Catalysed Arylation of Allylic Amides with Diaryliodonium Salts

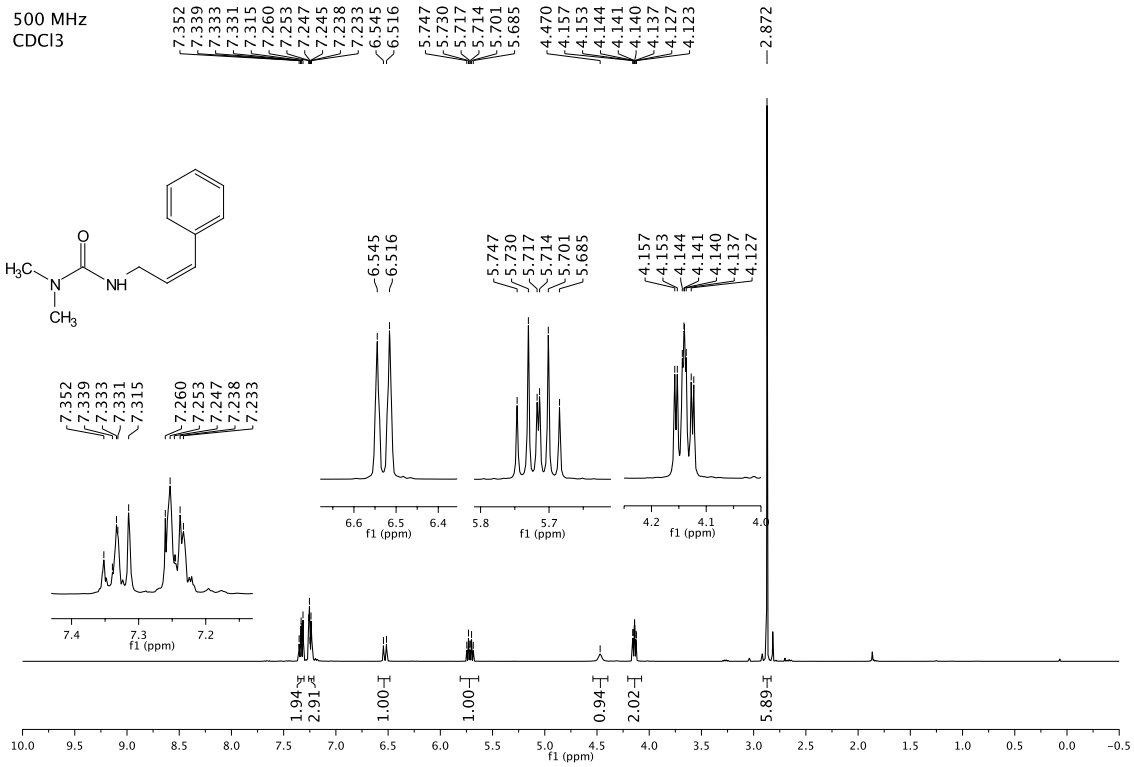
viii.1.1 Substrate synthesis

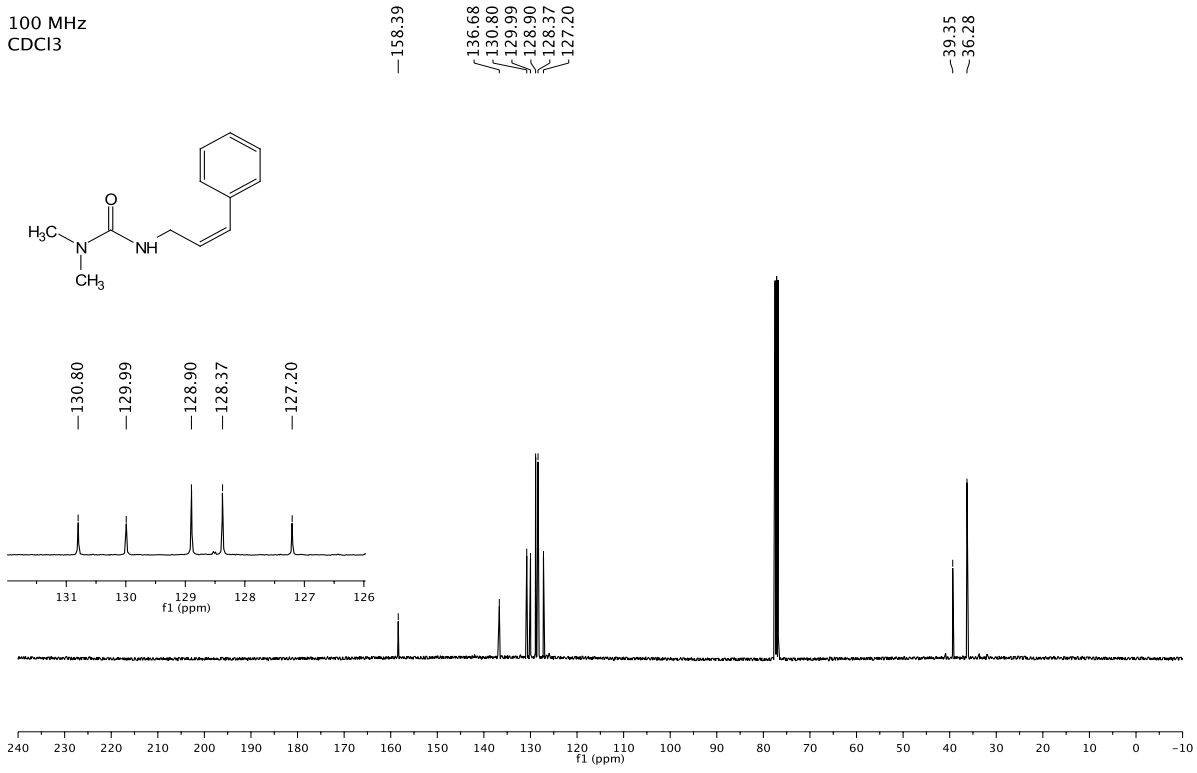
(Z)-3-phenylallyl pivalate **349**



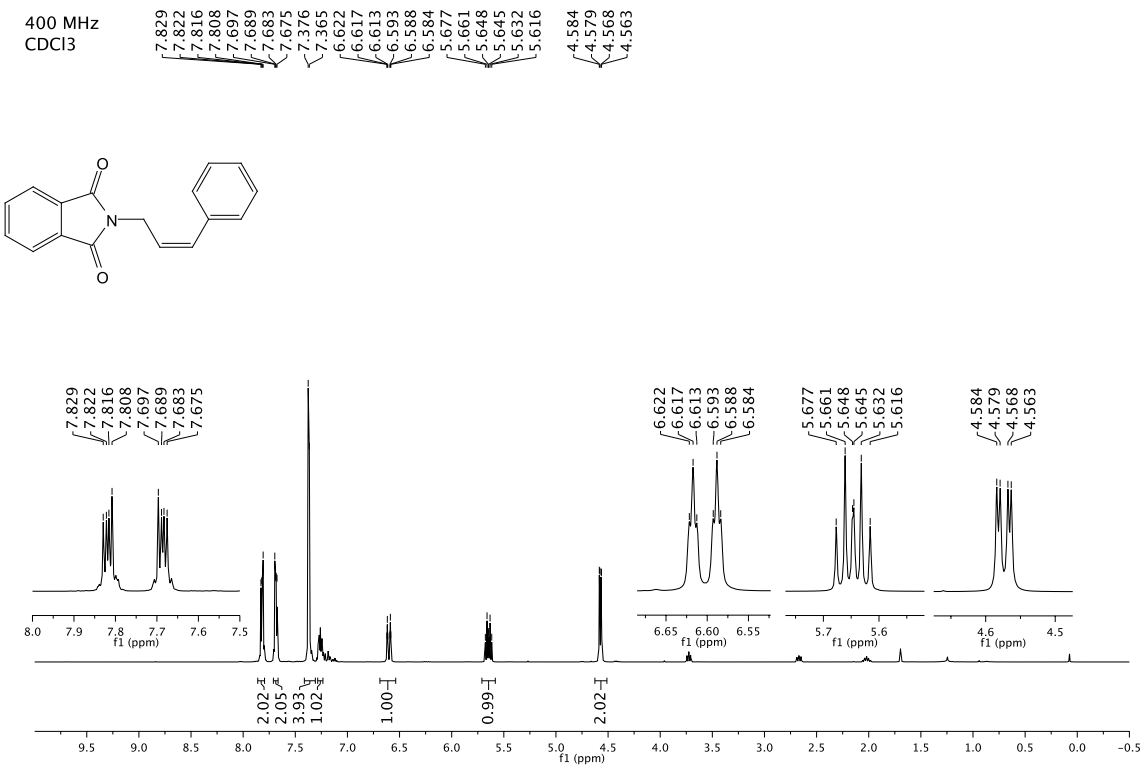


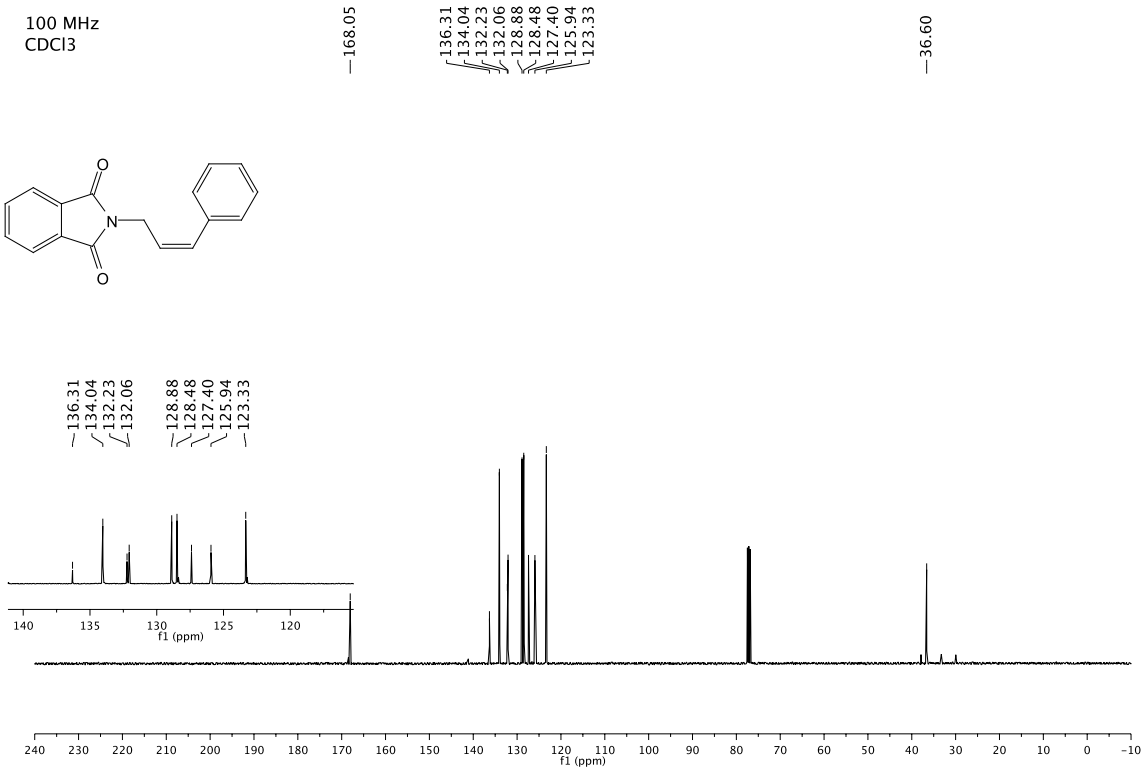
(Z)-1,1-dimethyl-3-(3-phenylallyl)urea **350**



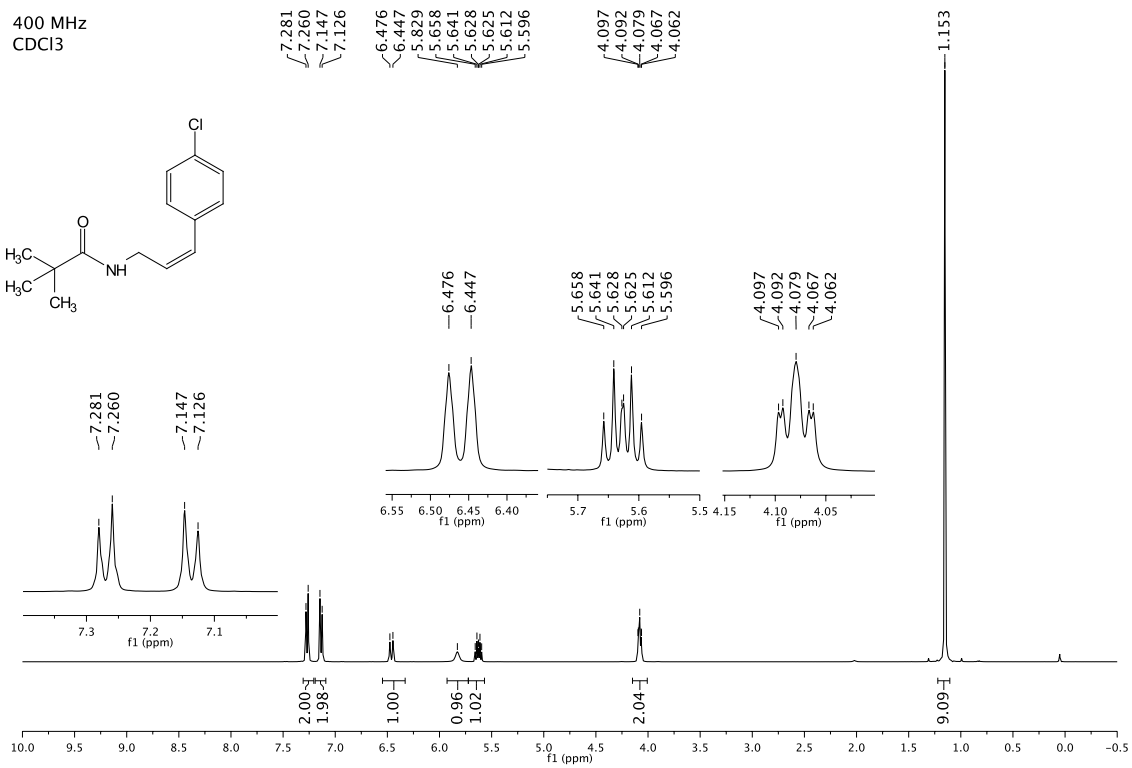


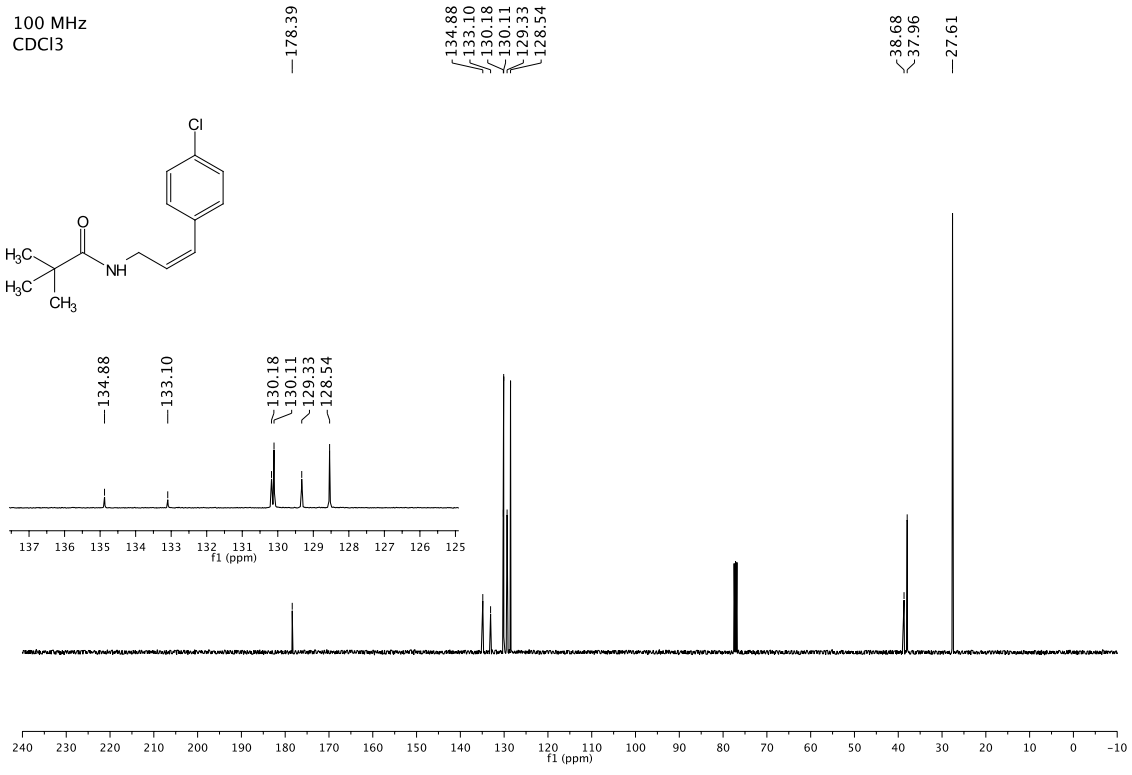
(Z)-2-(3-phenylallyl)isoindoline-1,3-dione **352**



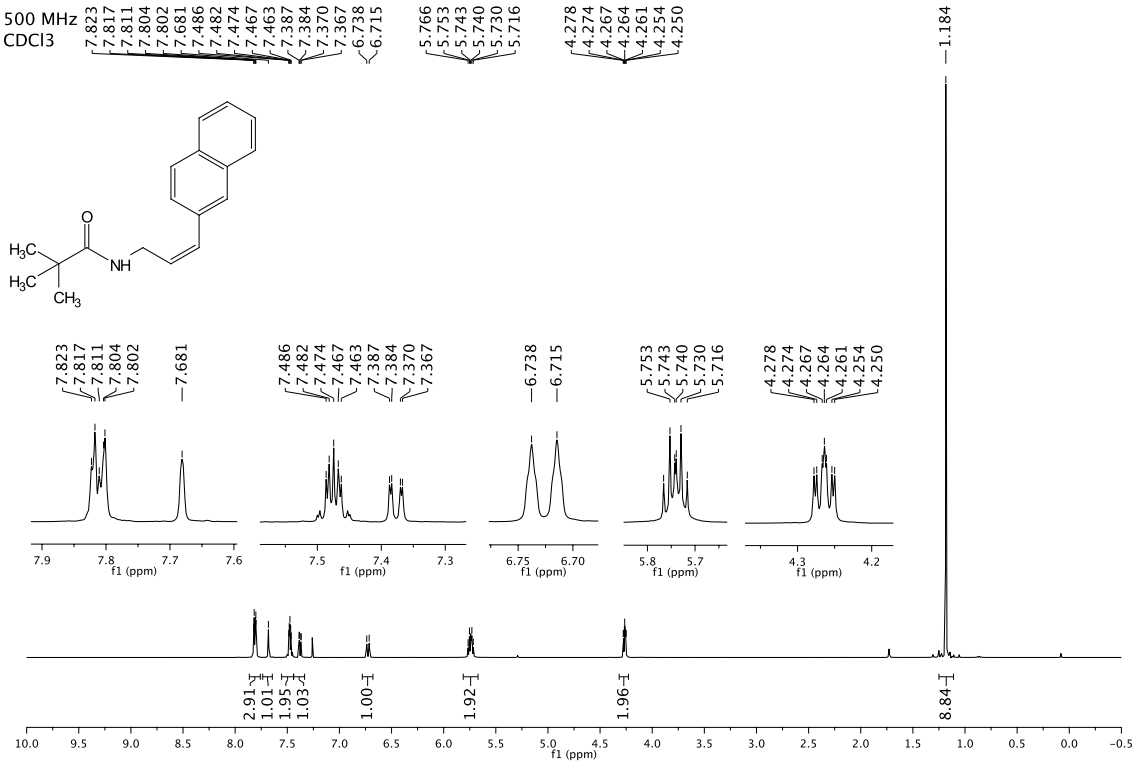


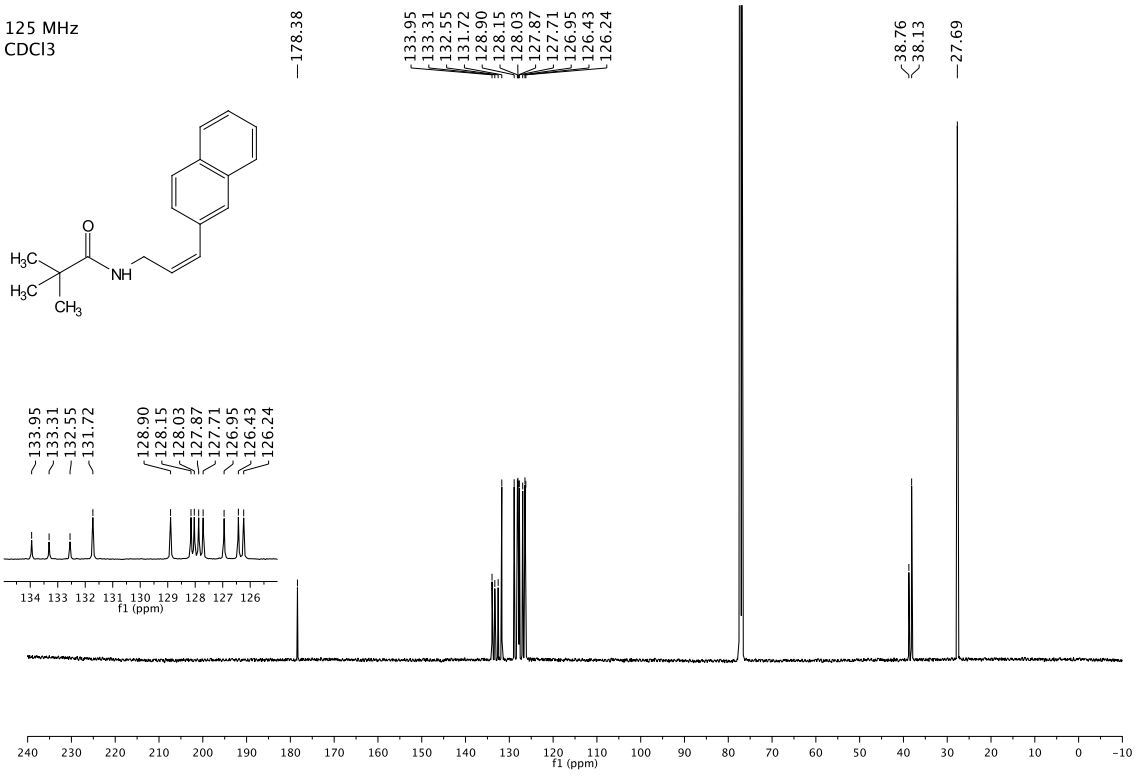
(Z)-N-(3-(4-chlorophenyl)allyl)pivalamide **356**



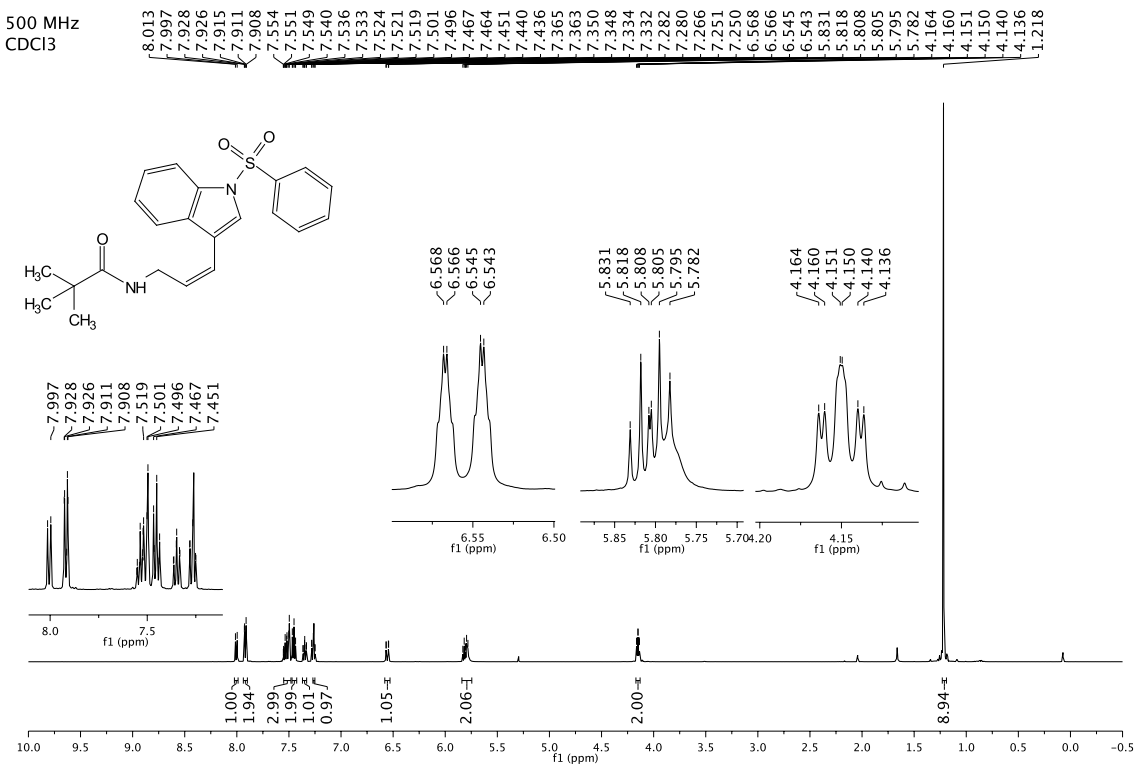


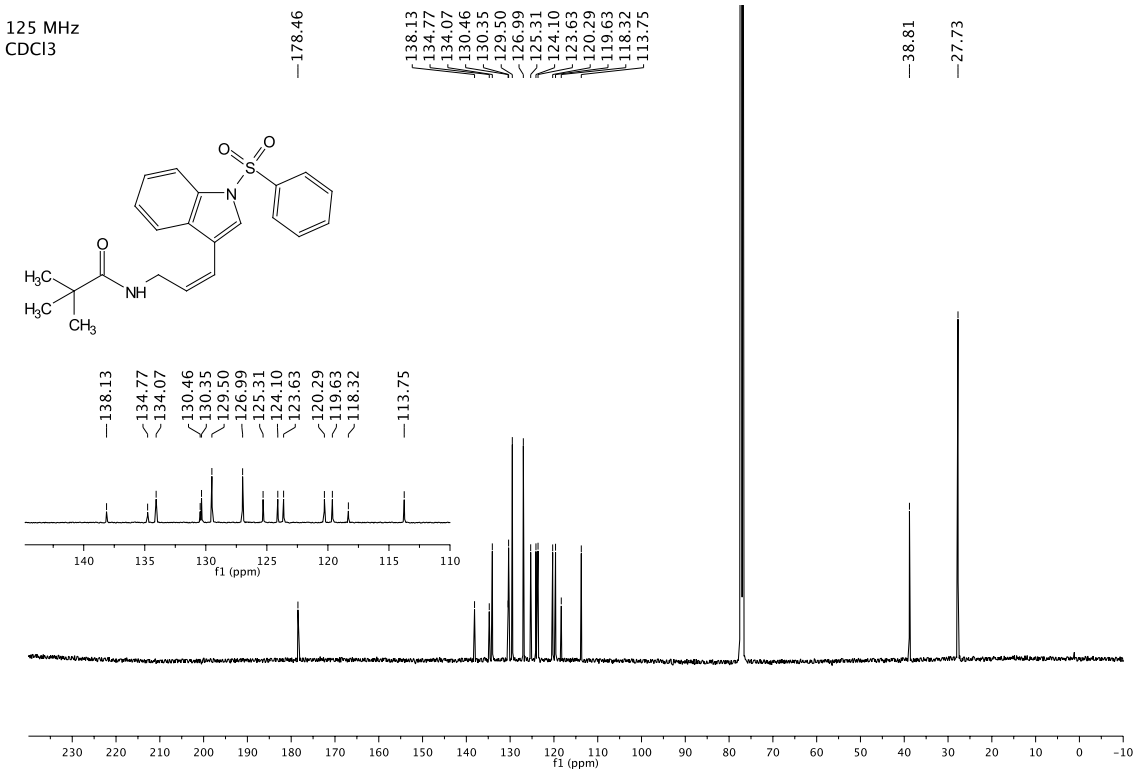
(Z)-N-(3-(naphthalen-2-yl)allyl)pivalamide **362**



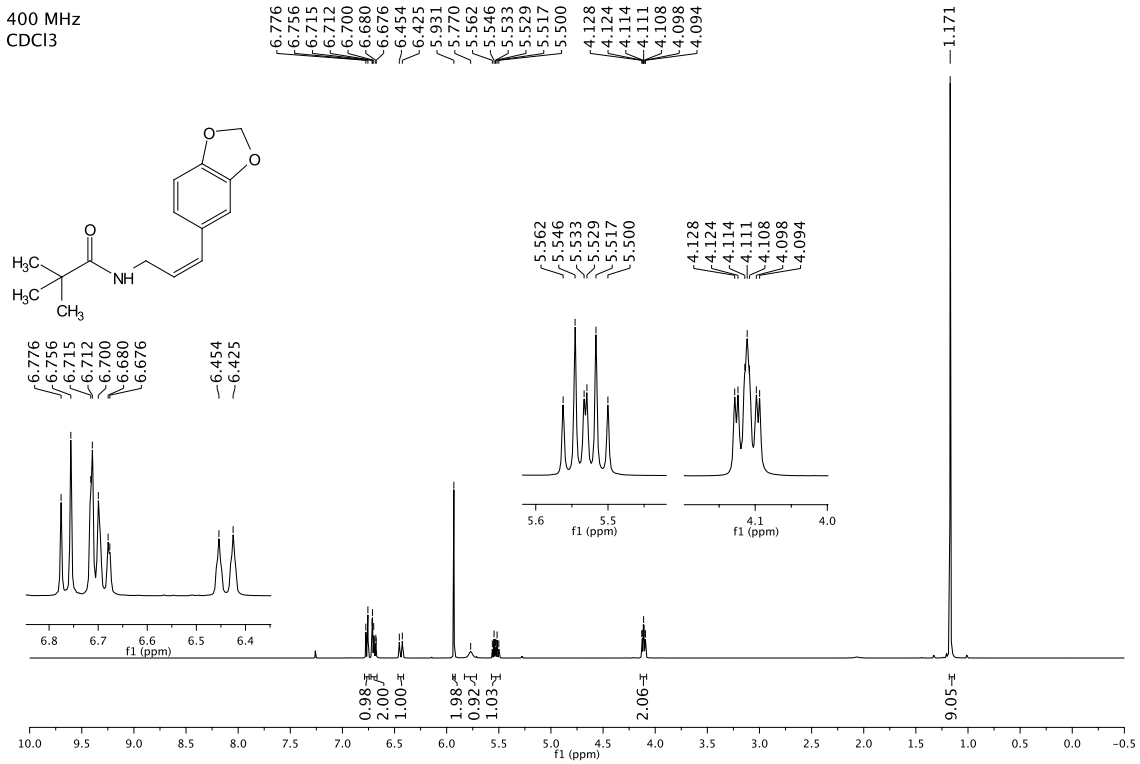


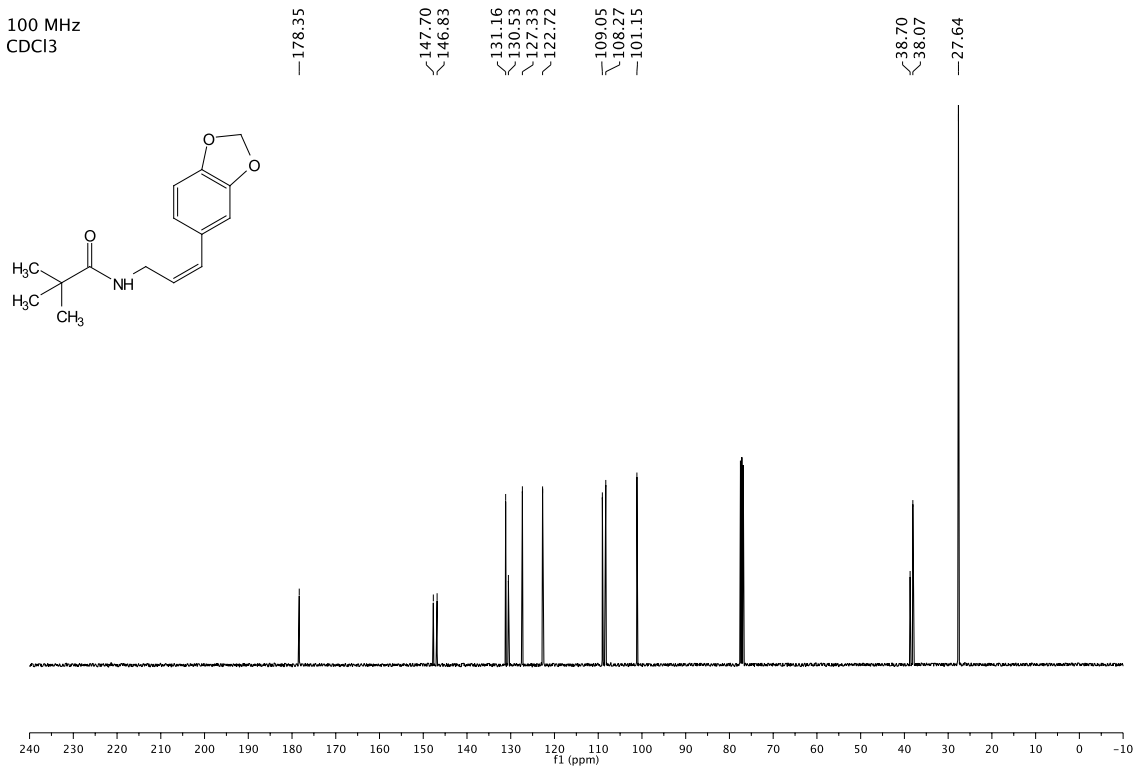
(Z)-N-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)allyl)pivalamide **364**



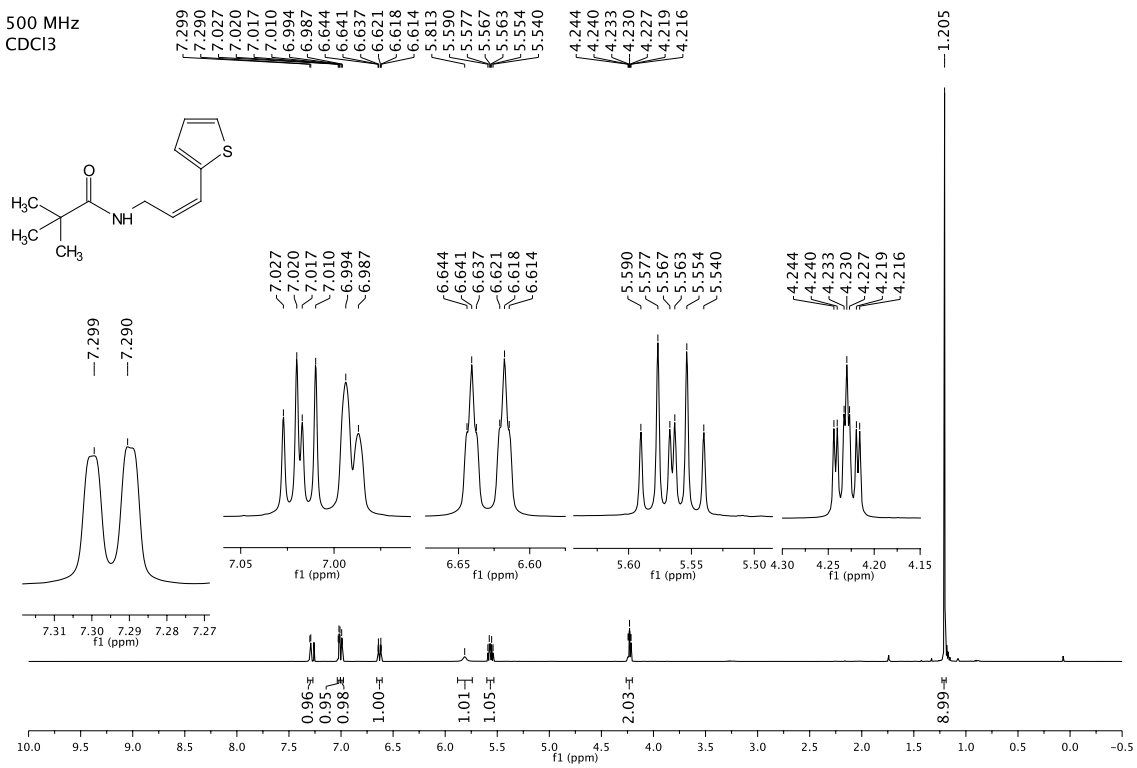


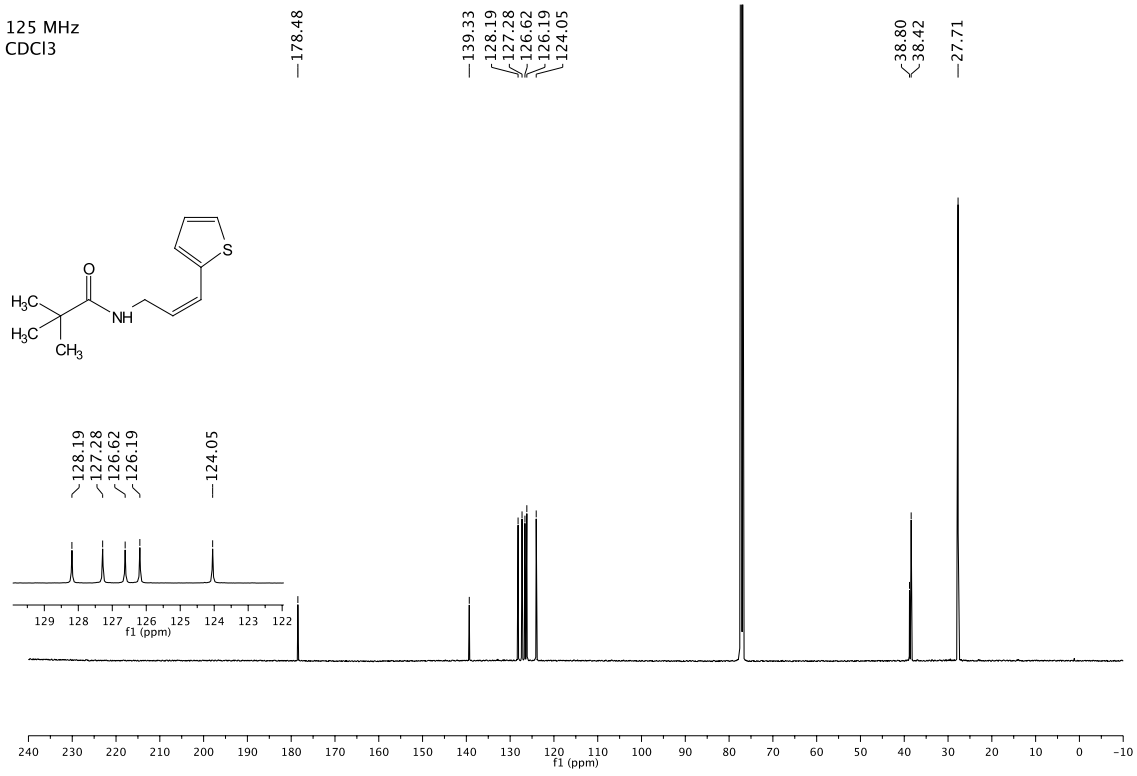
(Z)-N-(3-(benzo[d][1,3]dioxol-5-yl)allyl)pivalamide **365**





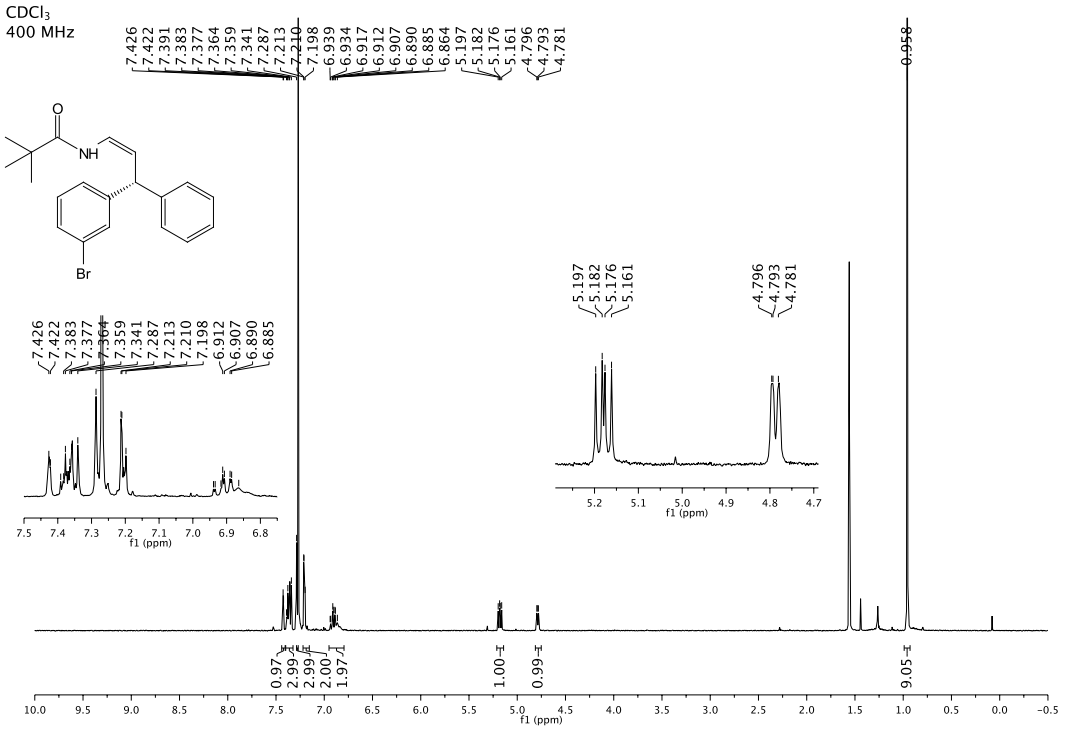
(Z)-N-(3-(thiophen-2-yl)allyl)pivalamide **366**

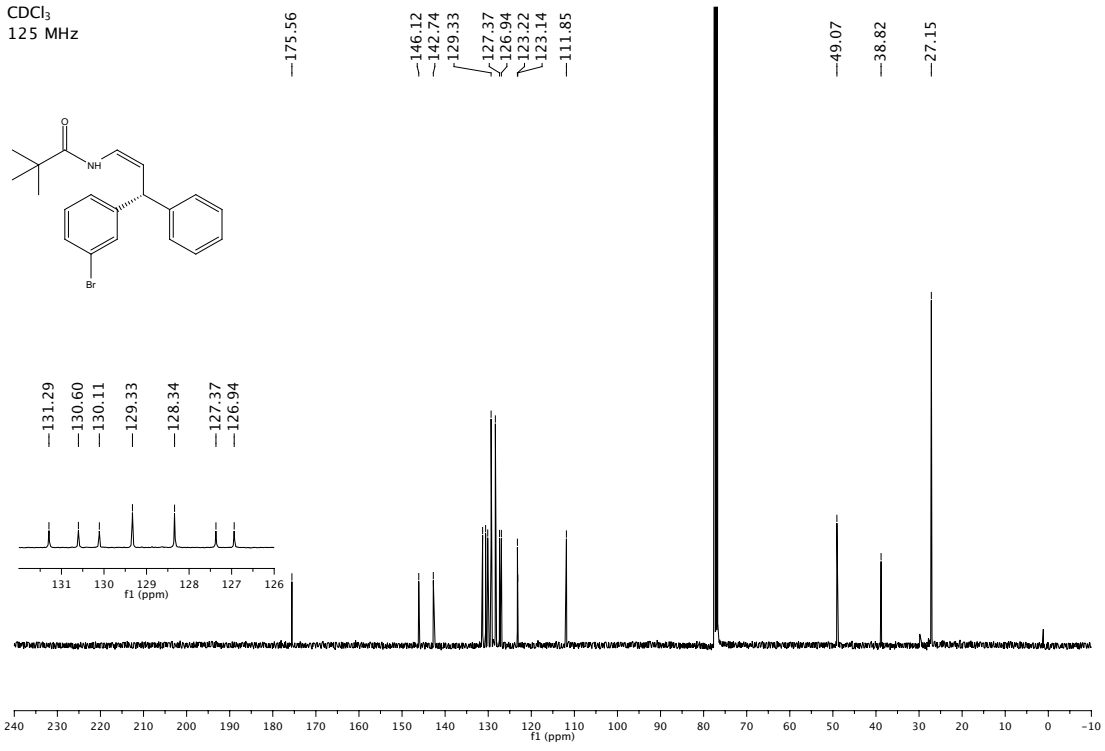




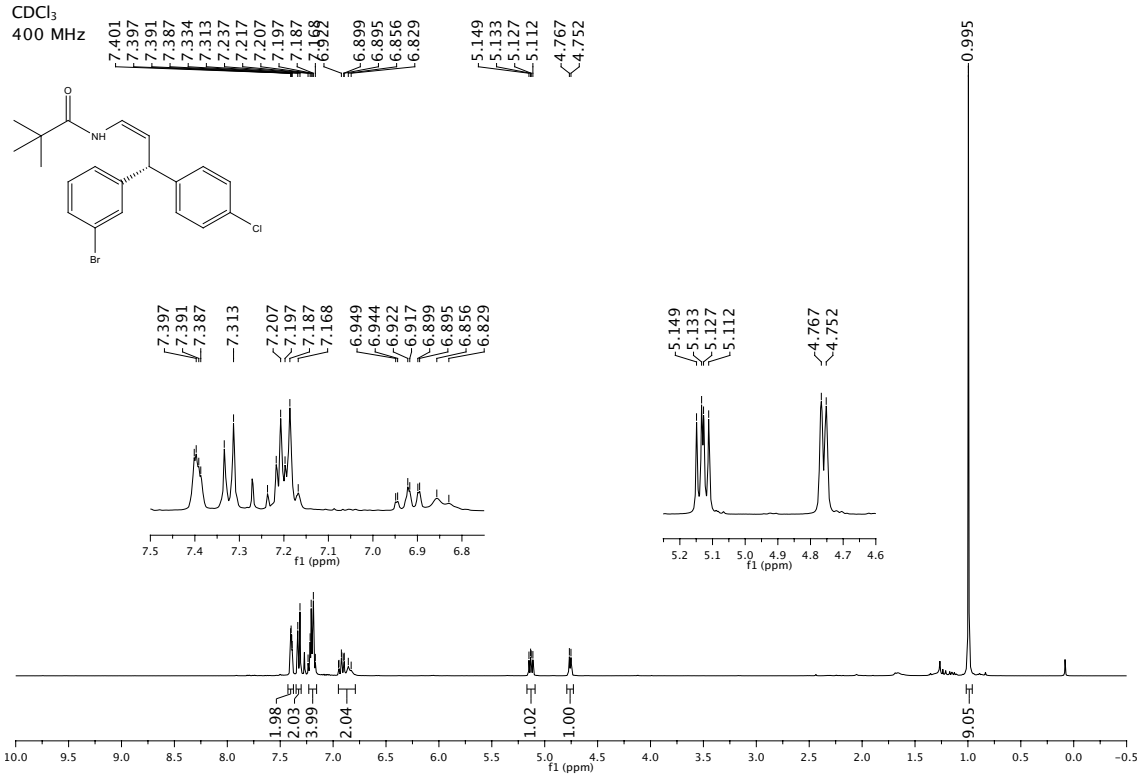
viii.1.2 Enamide products

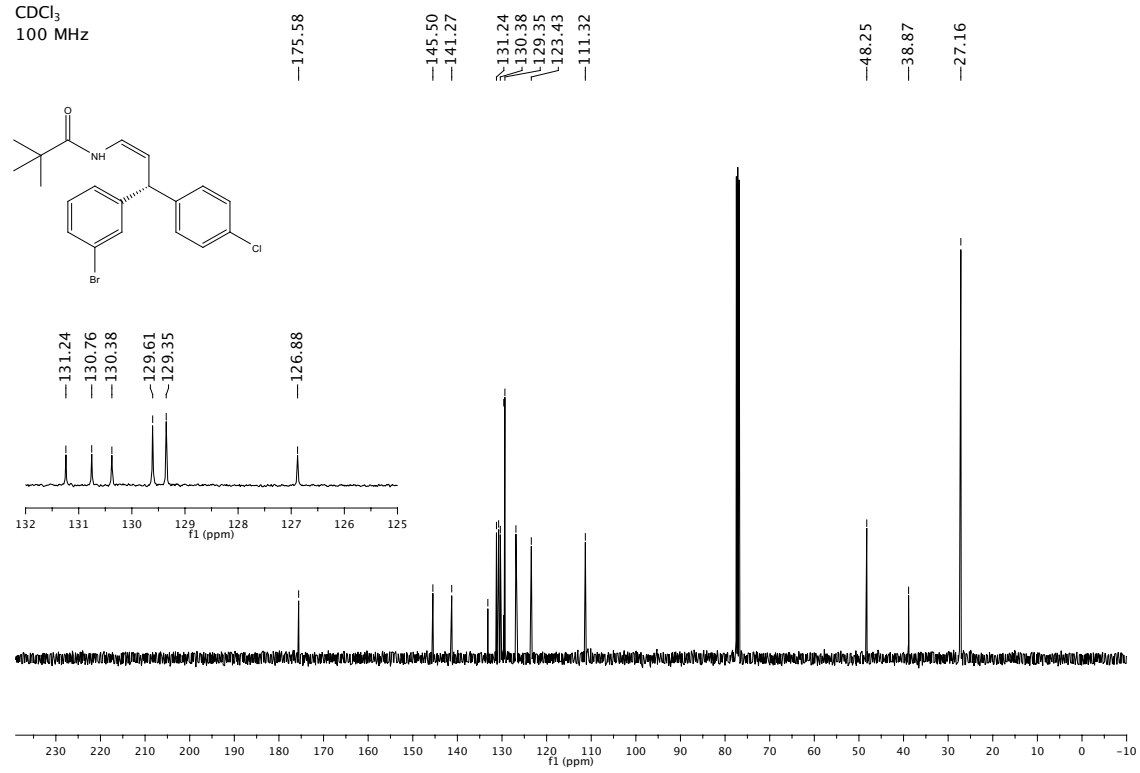
(R)-N-[(1Z)-3-(3-bromophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **332**



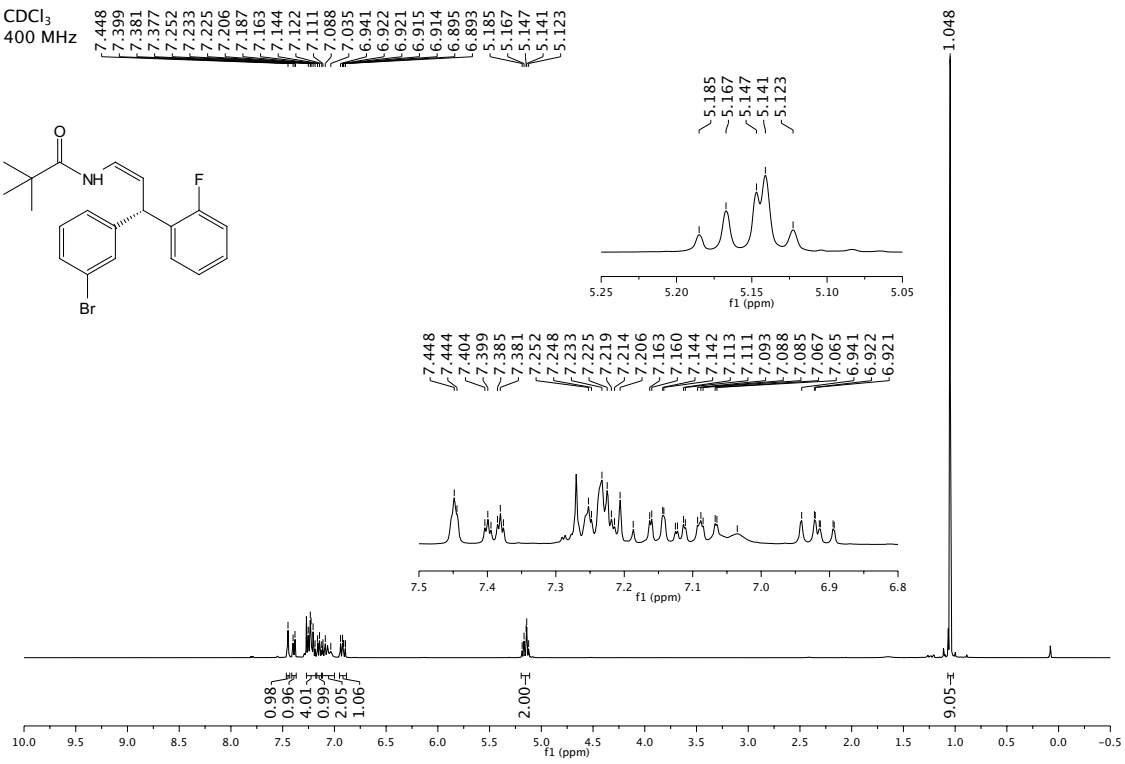


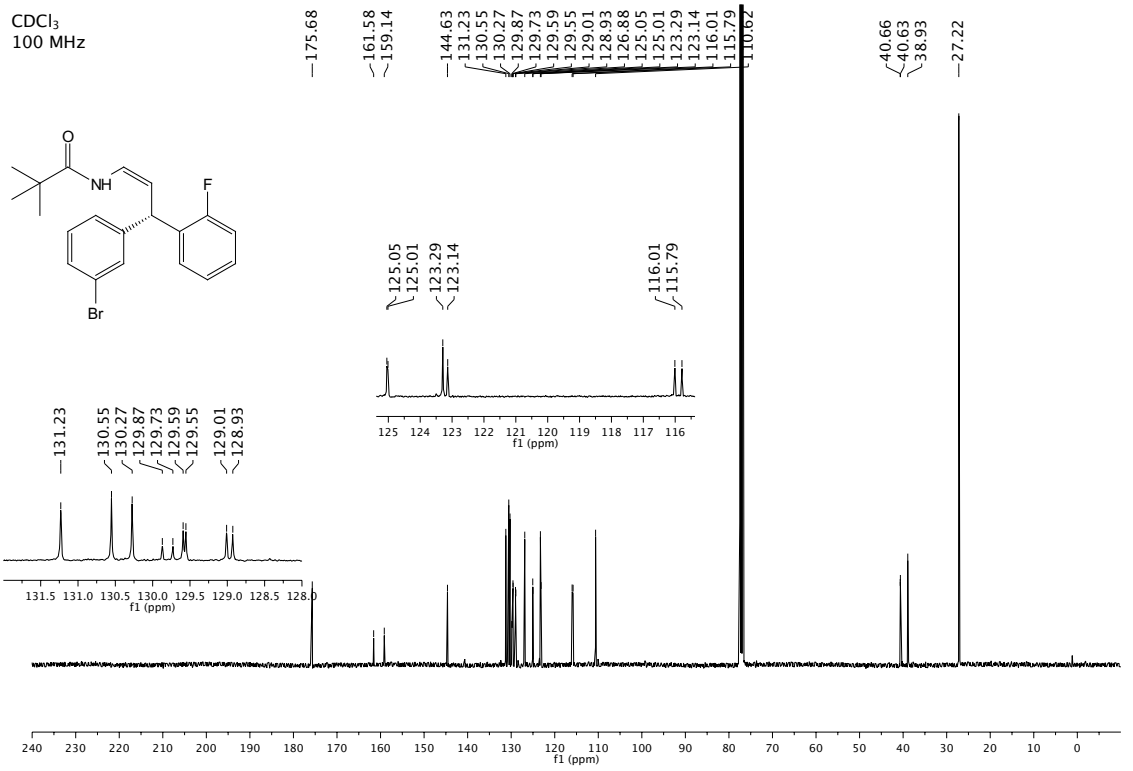
(R)-N-[(1Z)-3-(3-bromophenyl)-3-(4-chlorophenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **378**



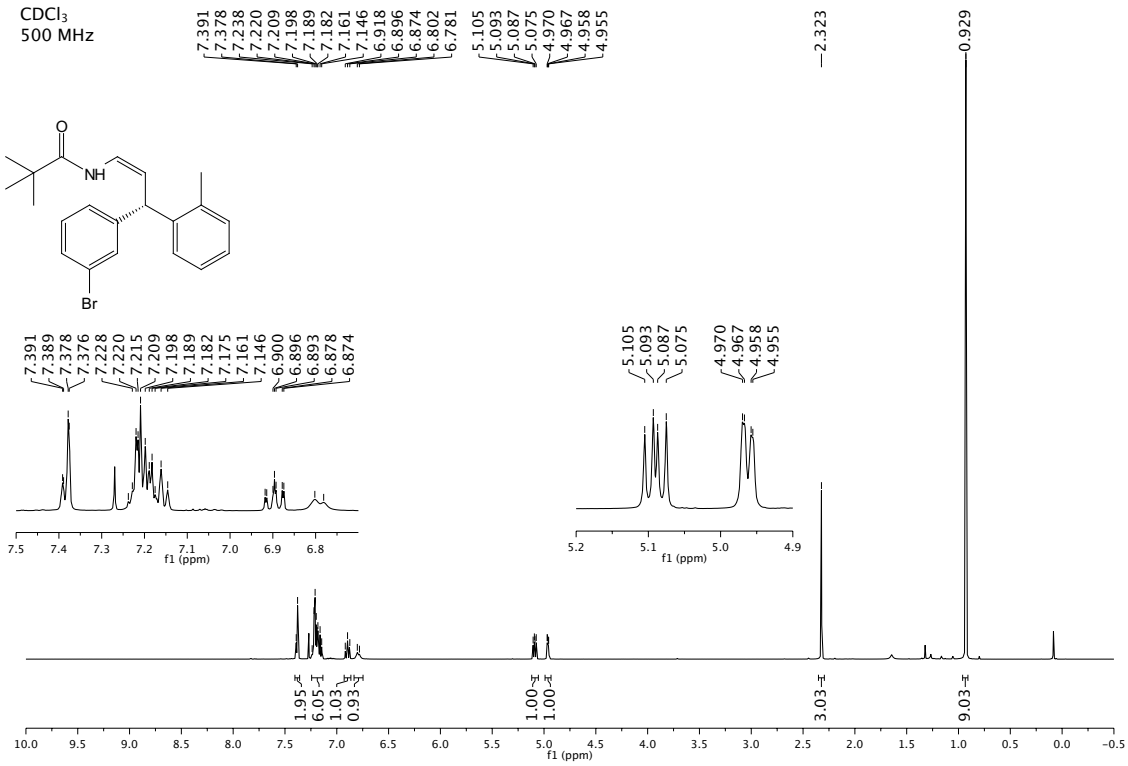


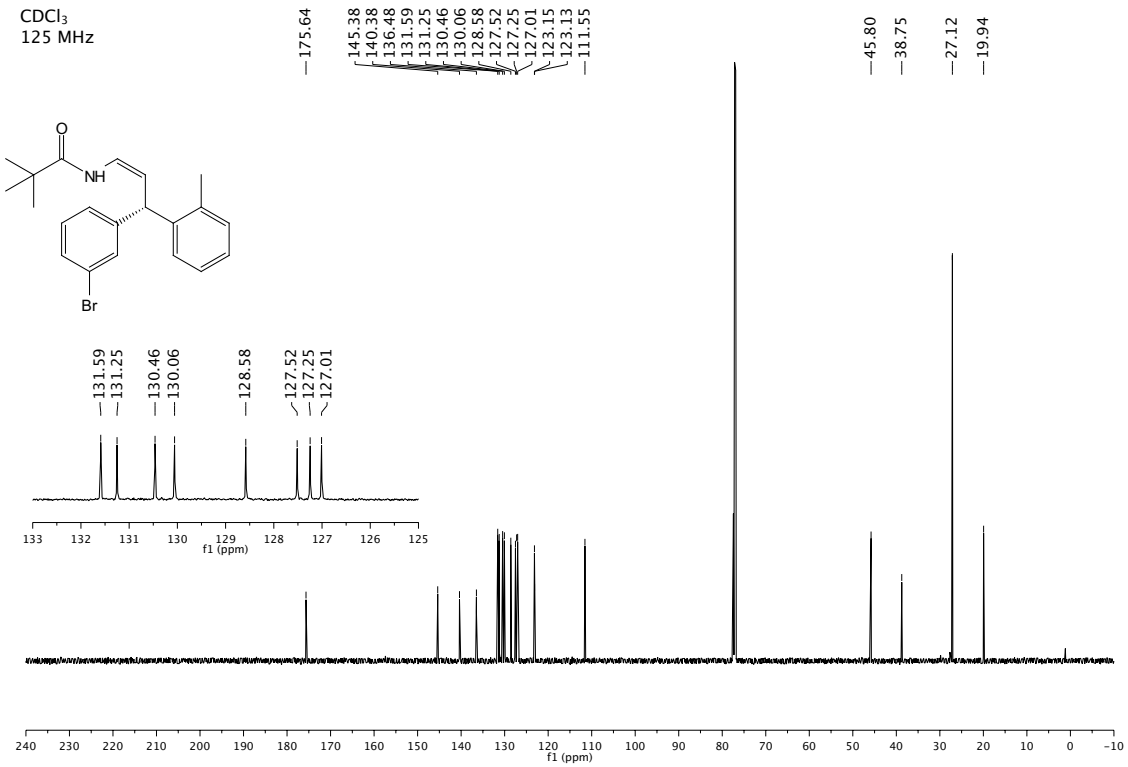
(S)-N-[(1Z)-3-(3-bromophenyl)-3-(2-fluorophenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **379**



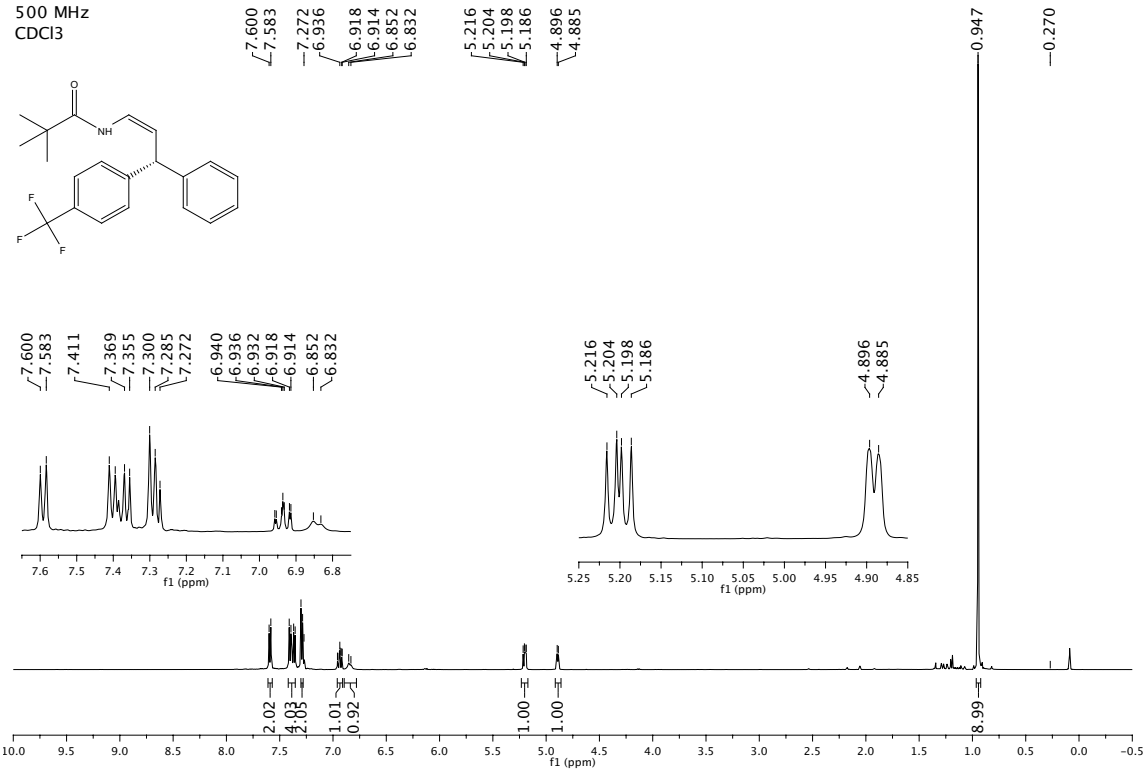


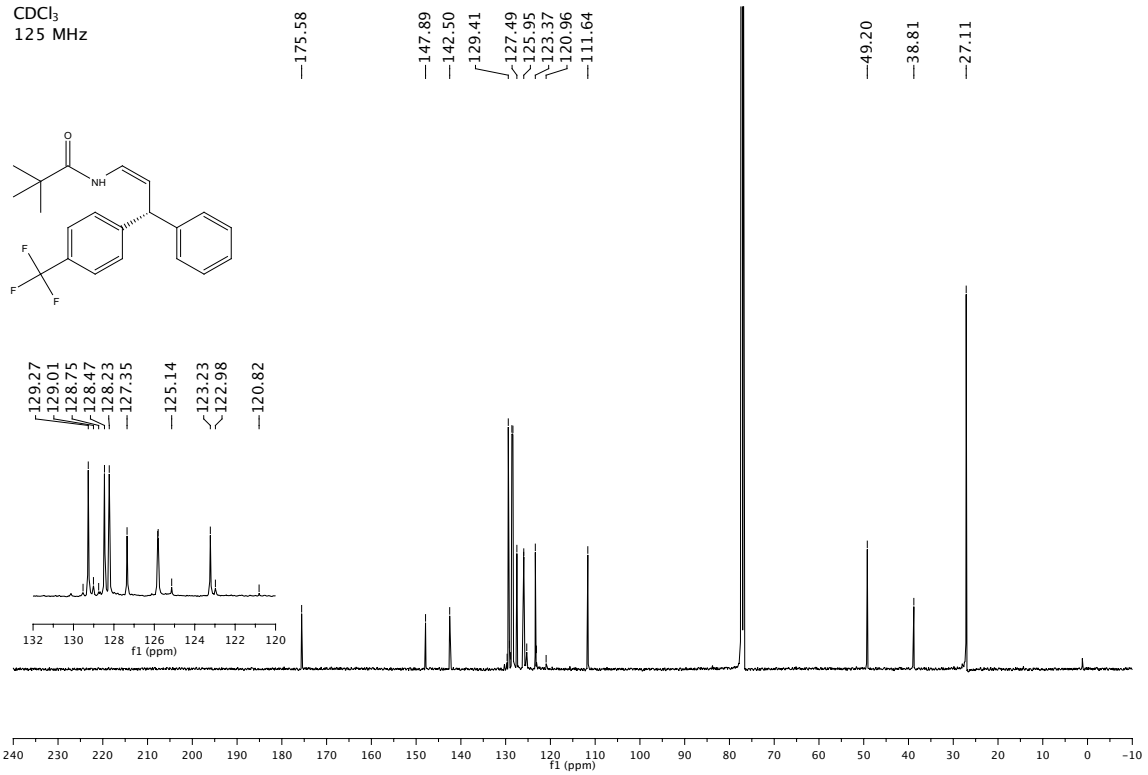
(S)-N-[(1Z)-3-(3-bromophenyl)-3-(2-methylphenyl)prop-1-en-1-yl]-2,2-dimethylpropanamide **380**



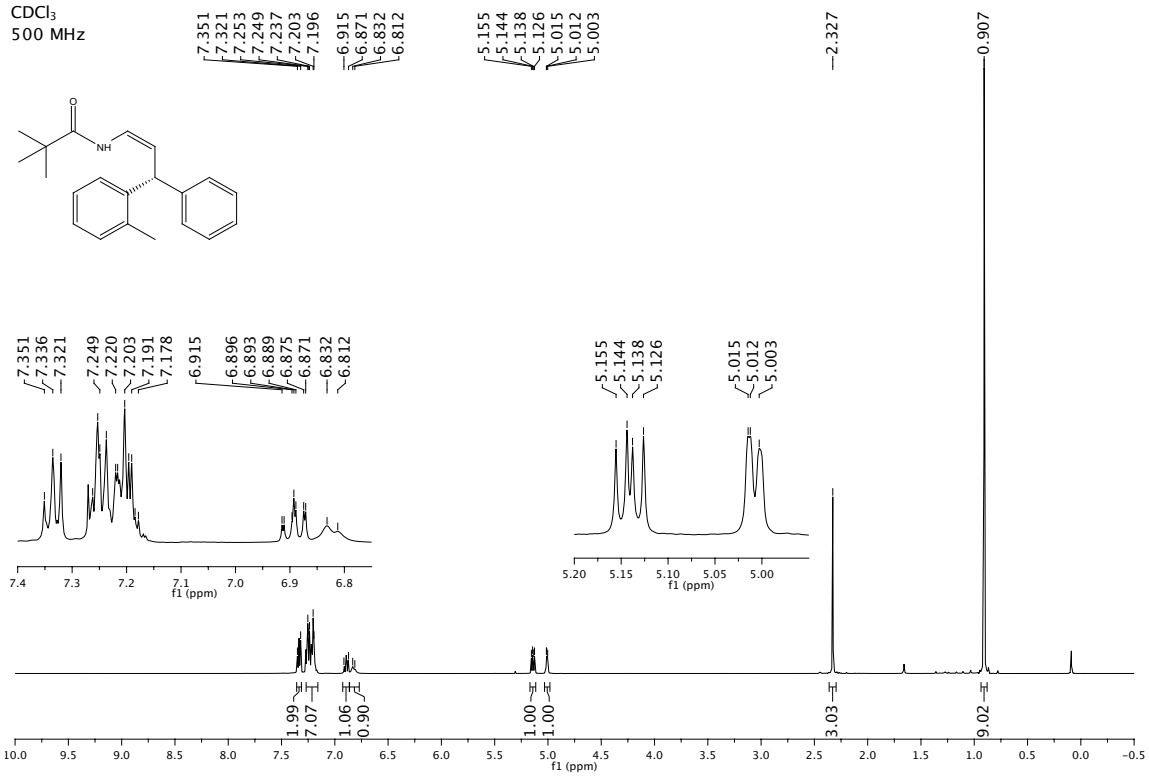


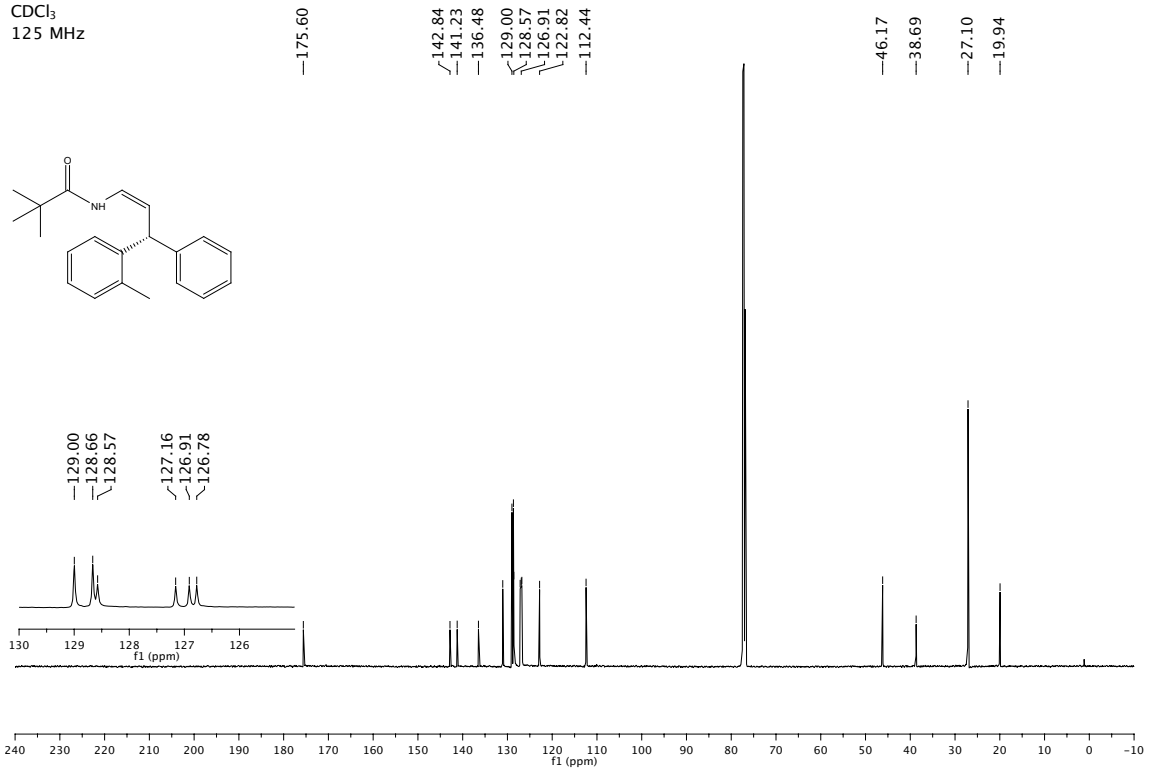
(R)-2,2-dimethyl-N-[(1Z)-3-phenyl-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **383**



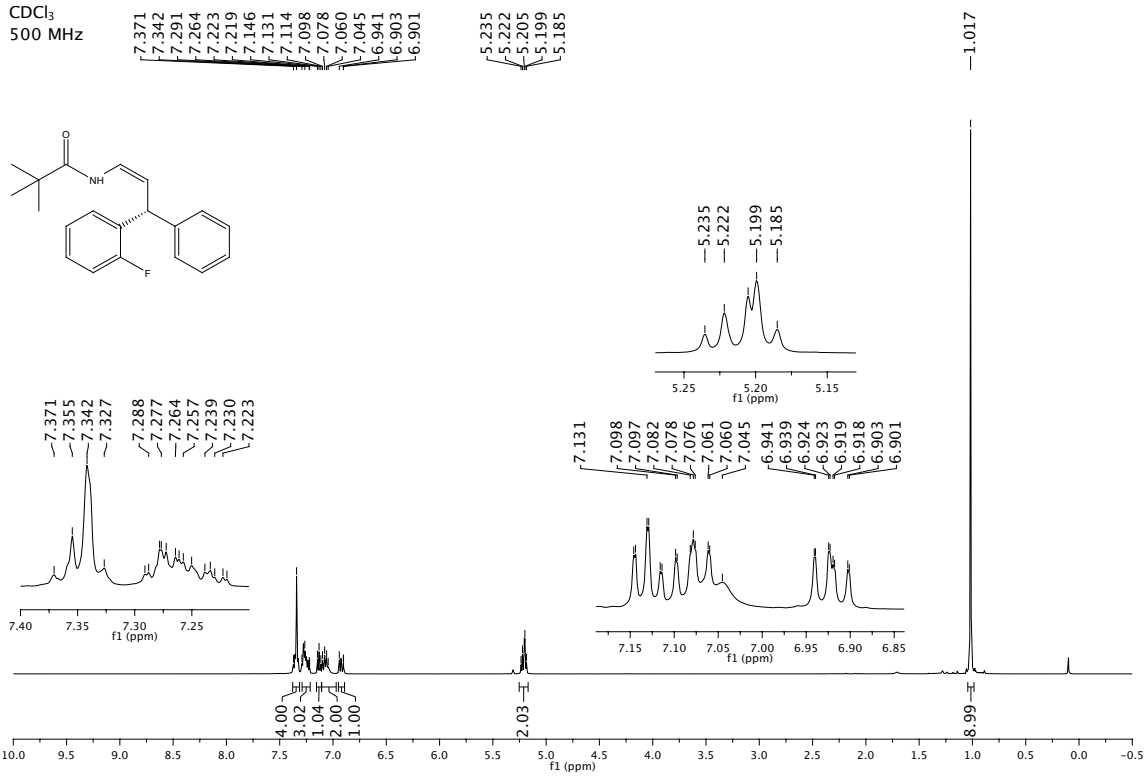


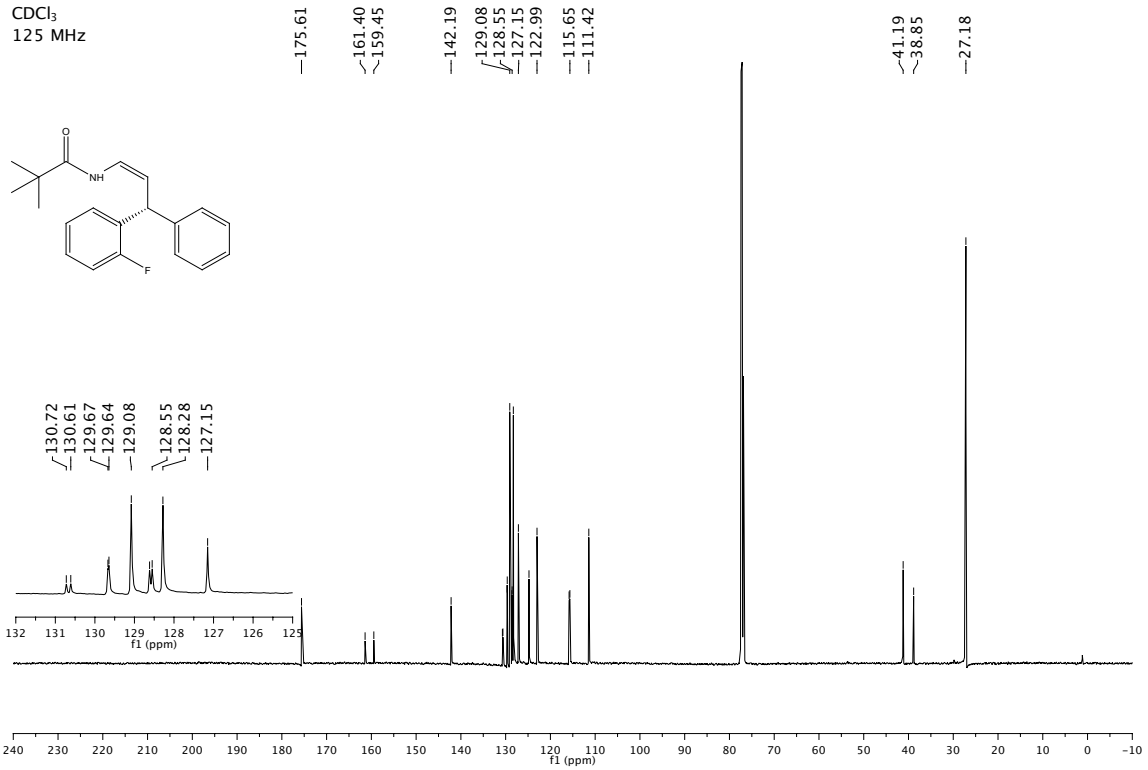
(R)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-phenylprop-1-en-1-yl]propanamide **384**



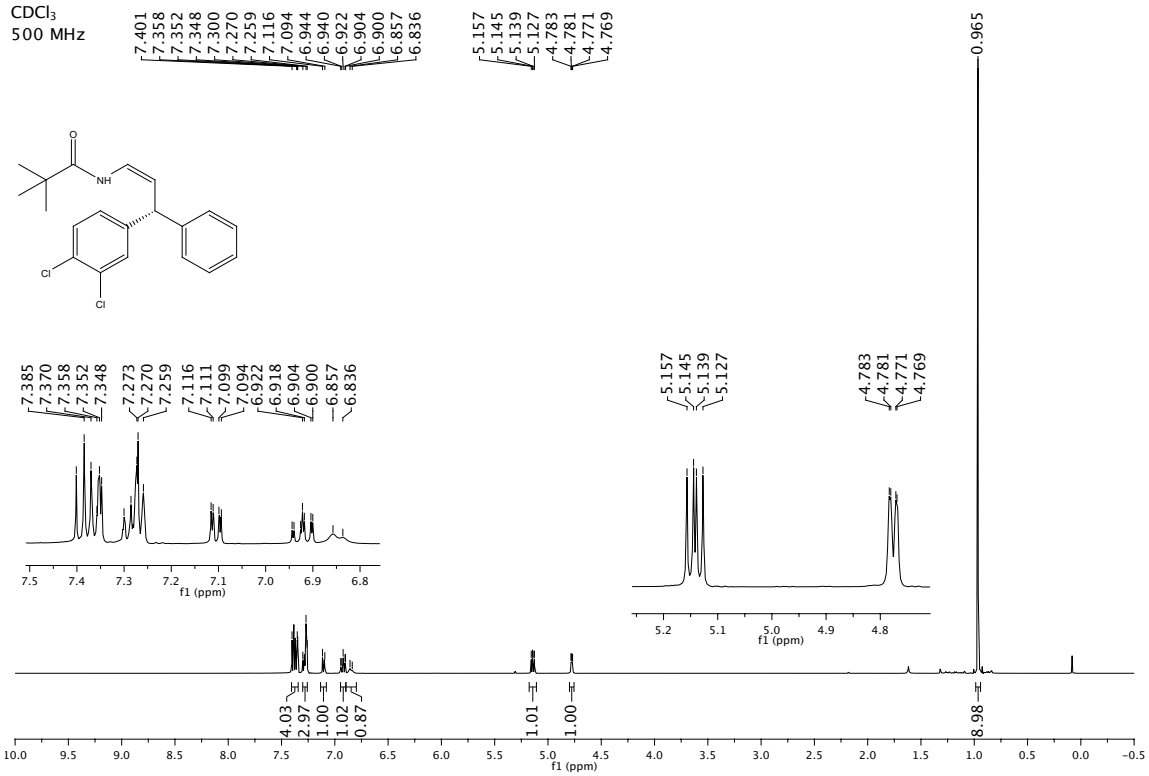


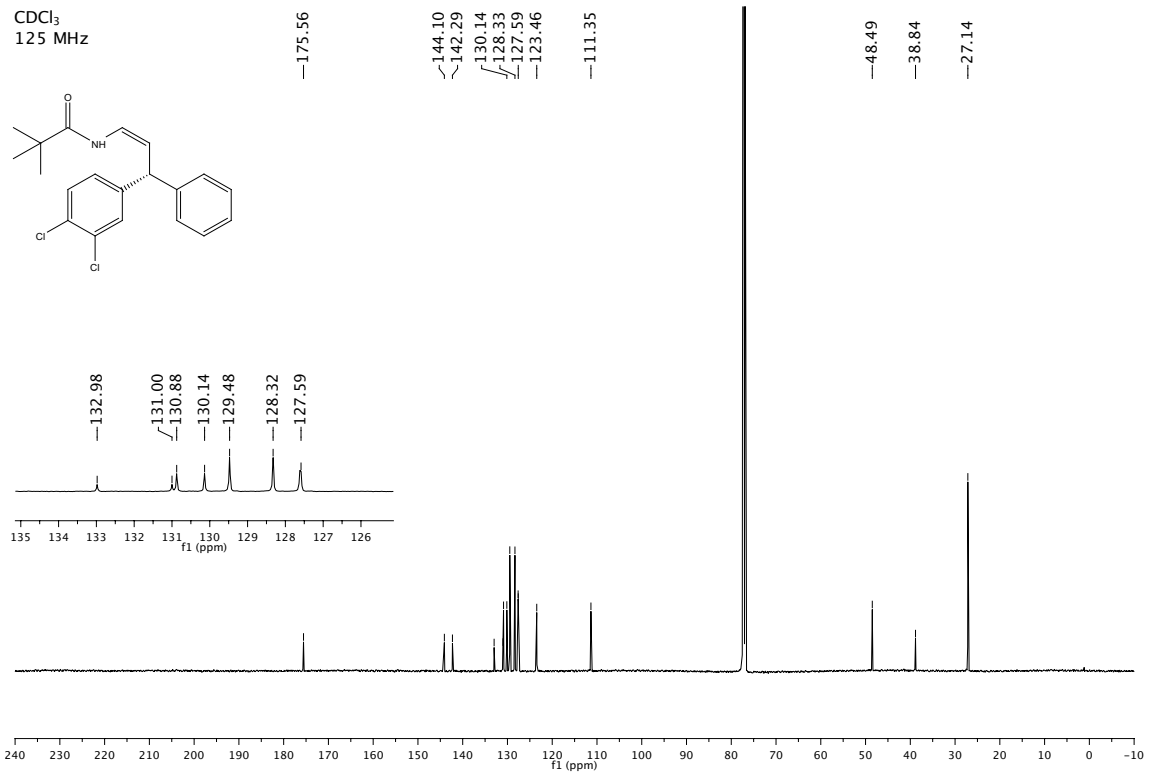
(R)-N-[(1Z)-3-(2-fluorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **385**



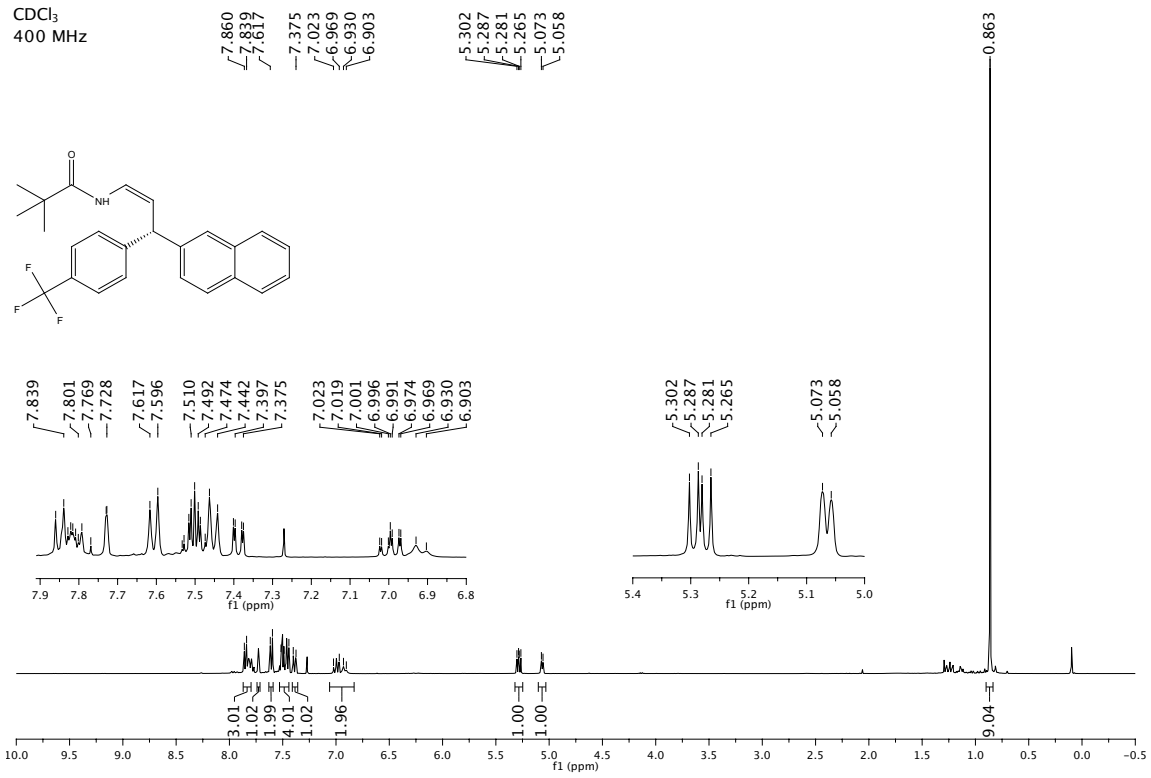


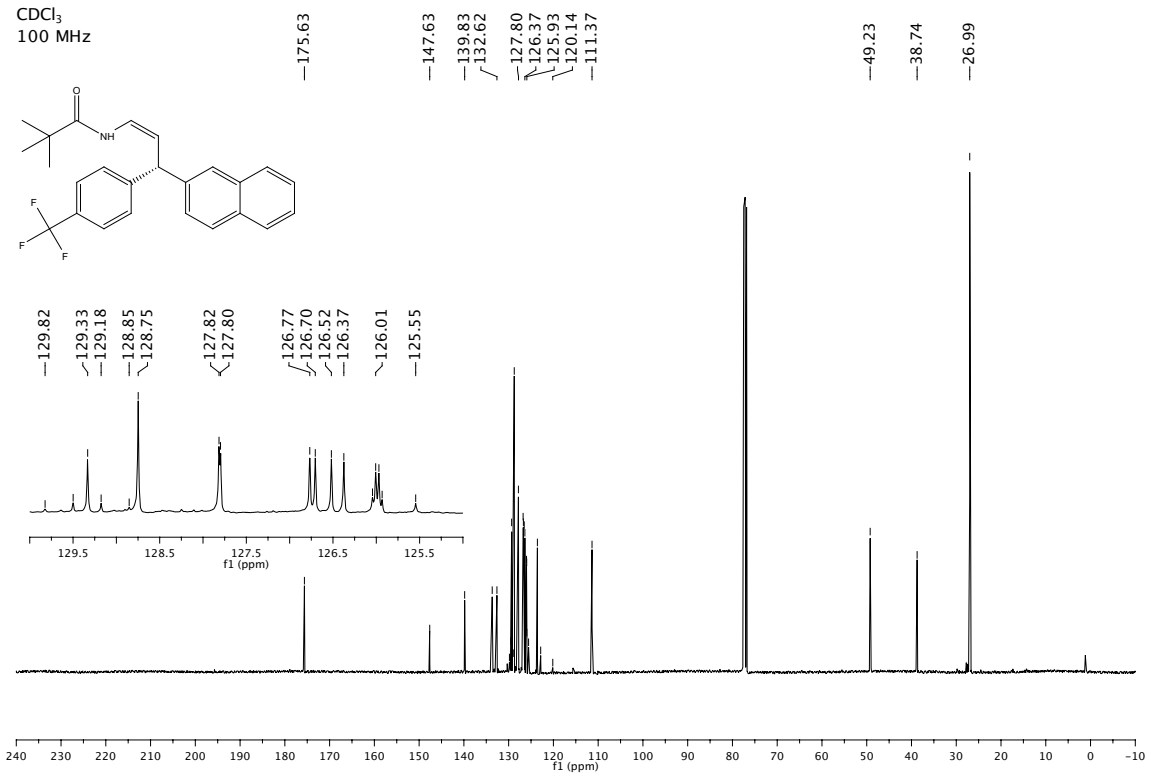
(R)-N-[(1Z)-3-(3,4-dichlorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **389**



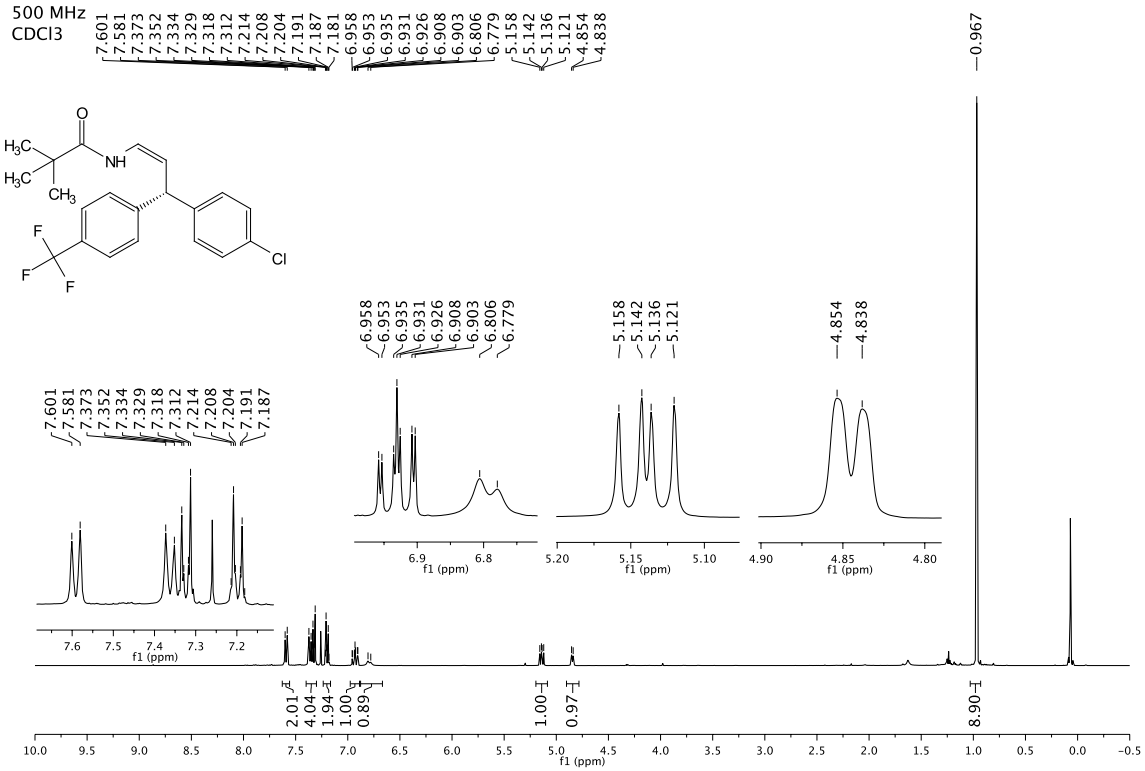


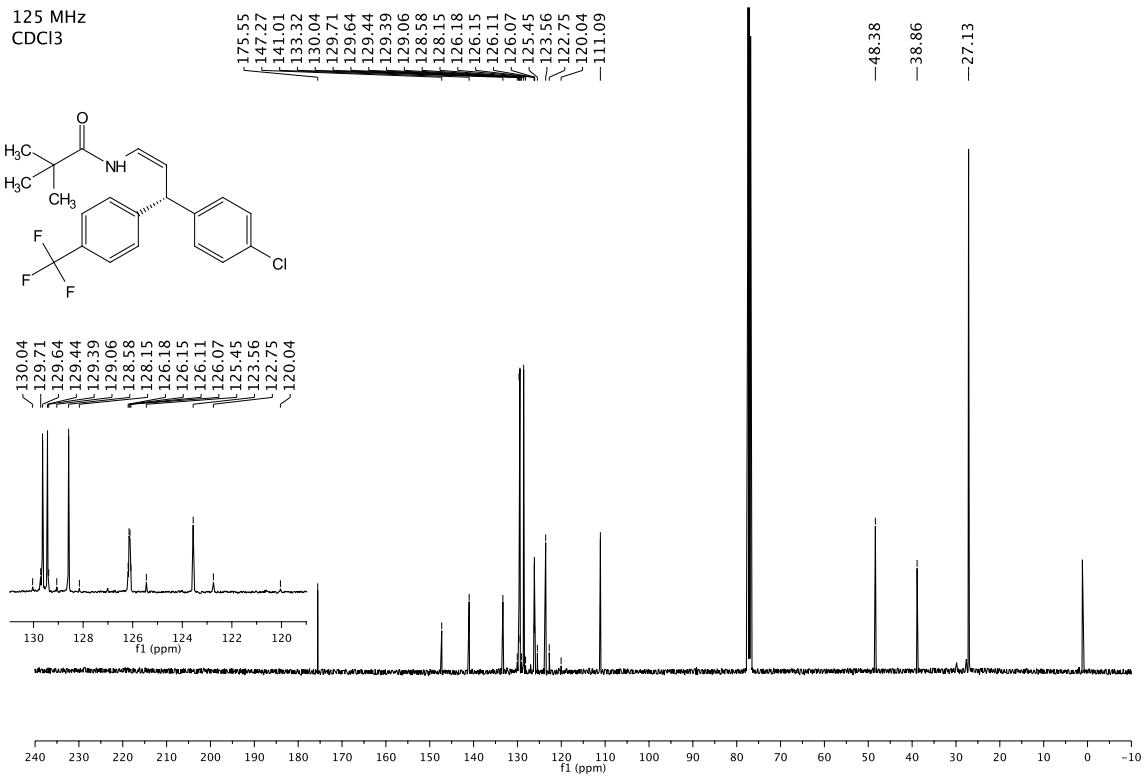
(S)-2,2-dimethyl-N-[(1Z)-3-(naphthalen-2-yl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **396**



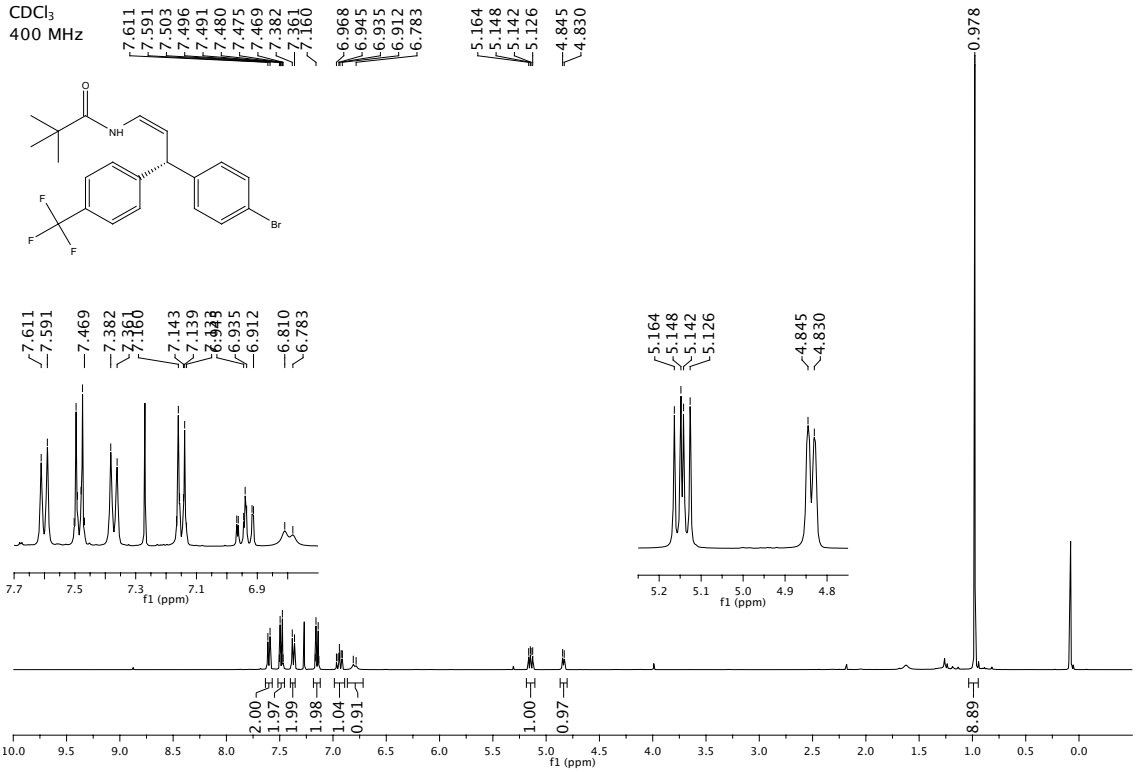


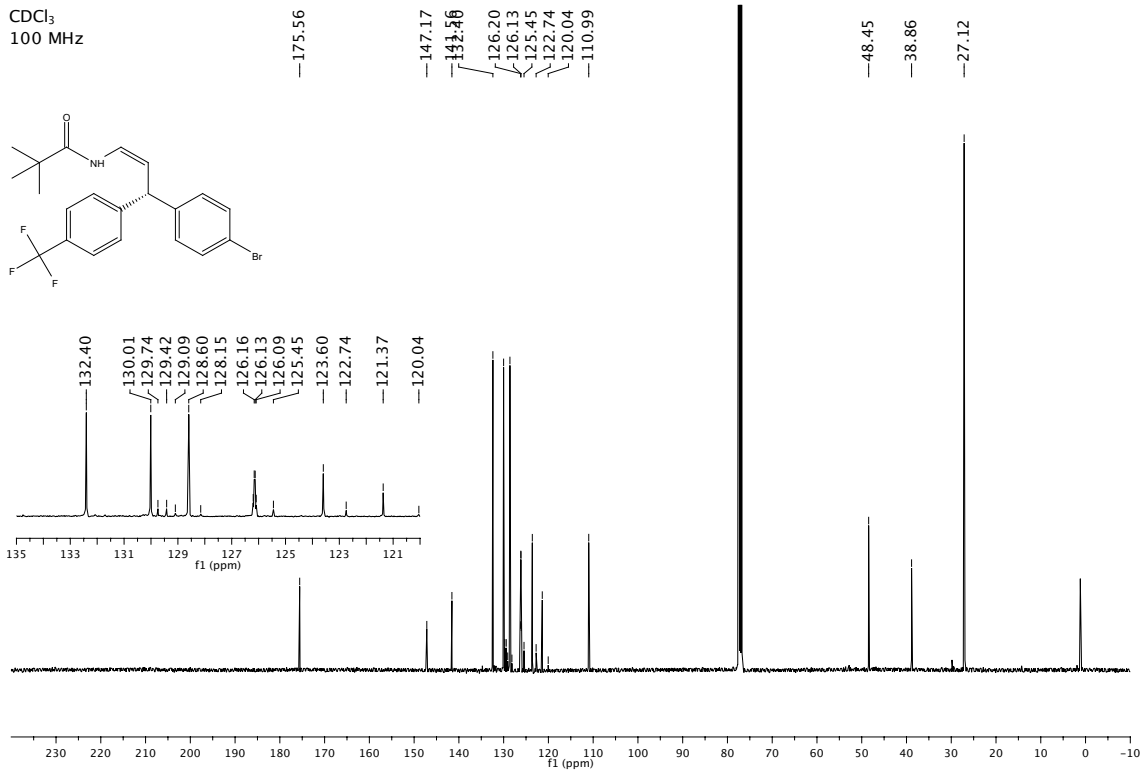
(S)-N-[(1Z)-3-(4-chlorophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **398**



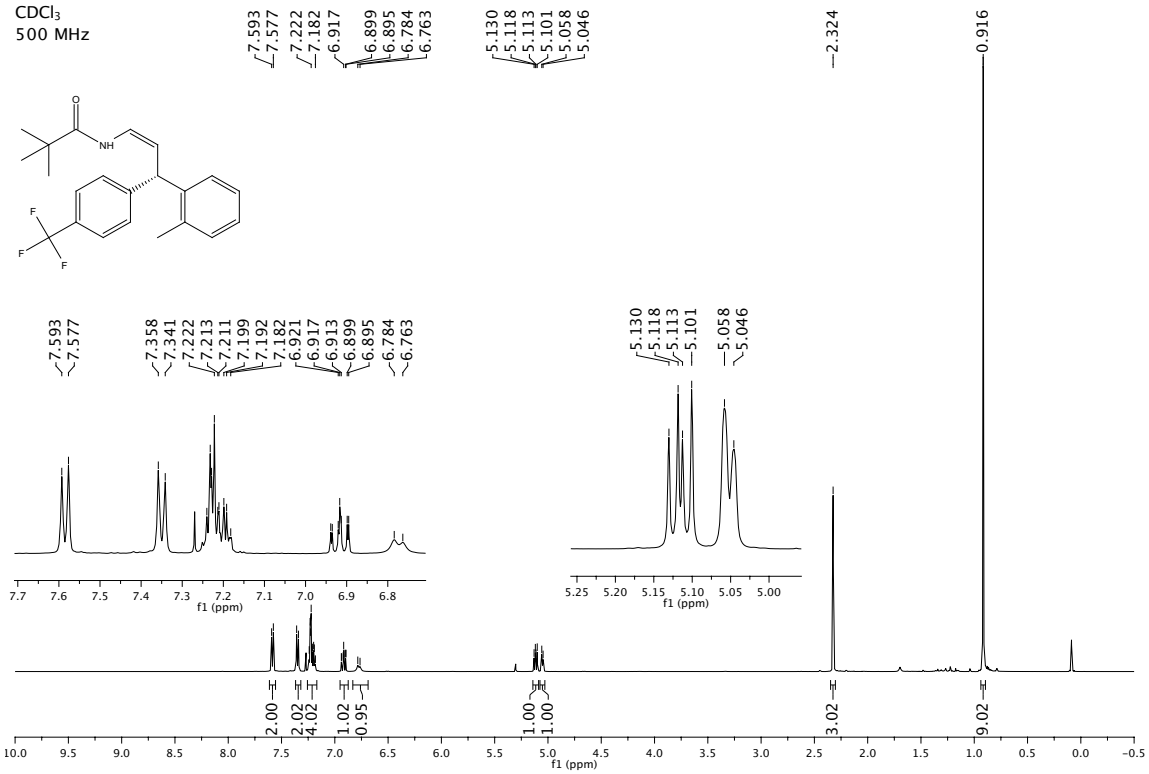


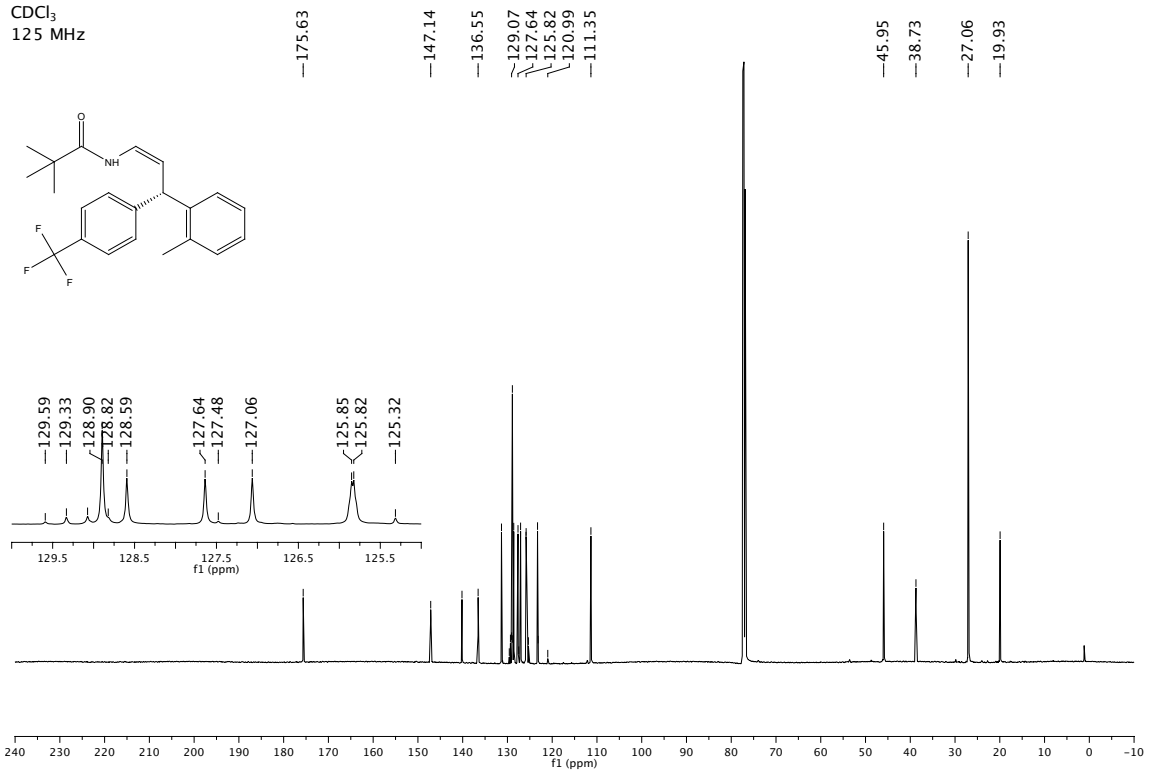
(S)-N-[(1Z)-3-(4-bromophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **399**



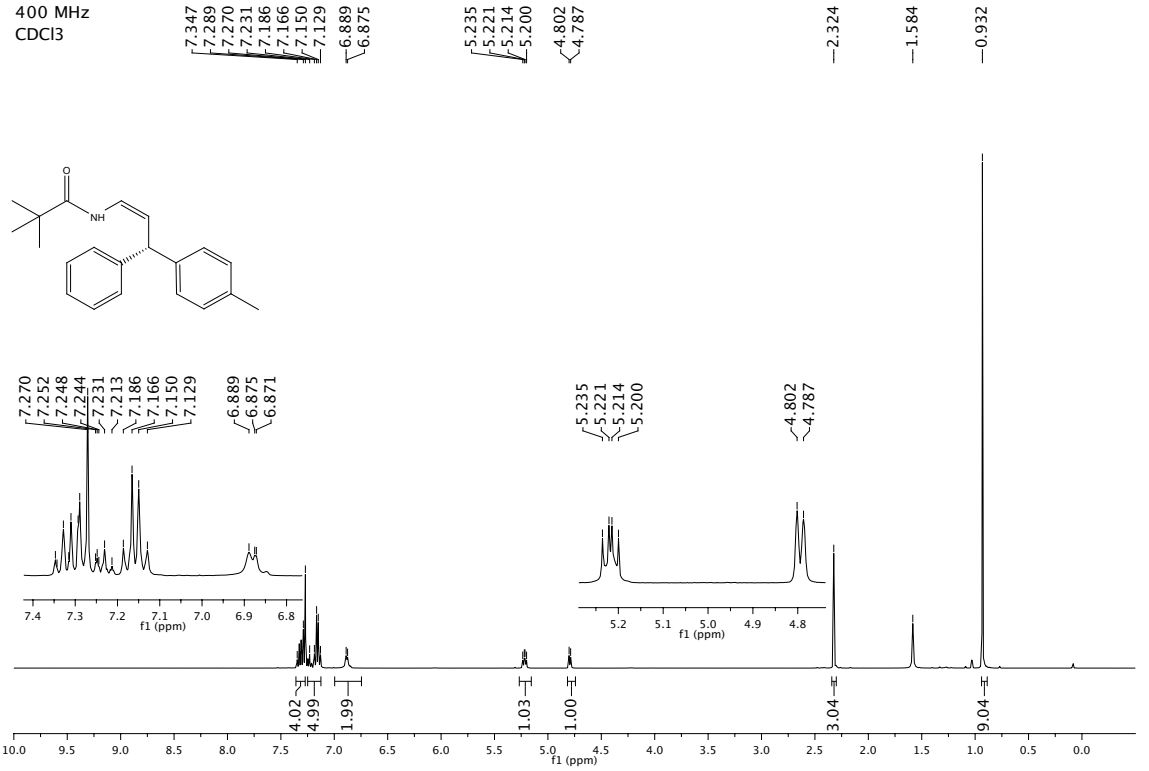


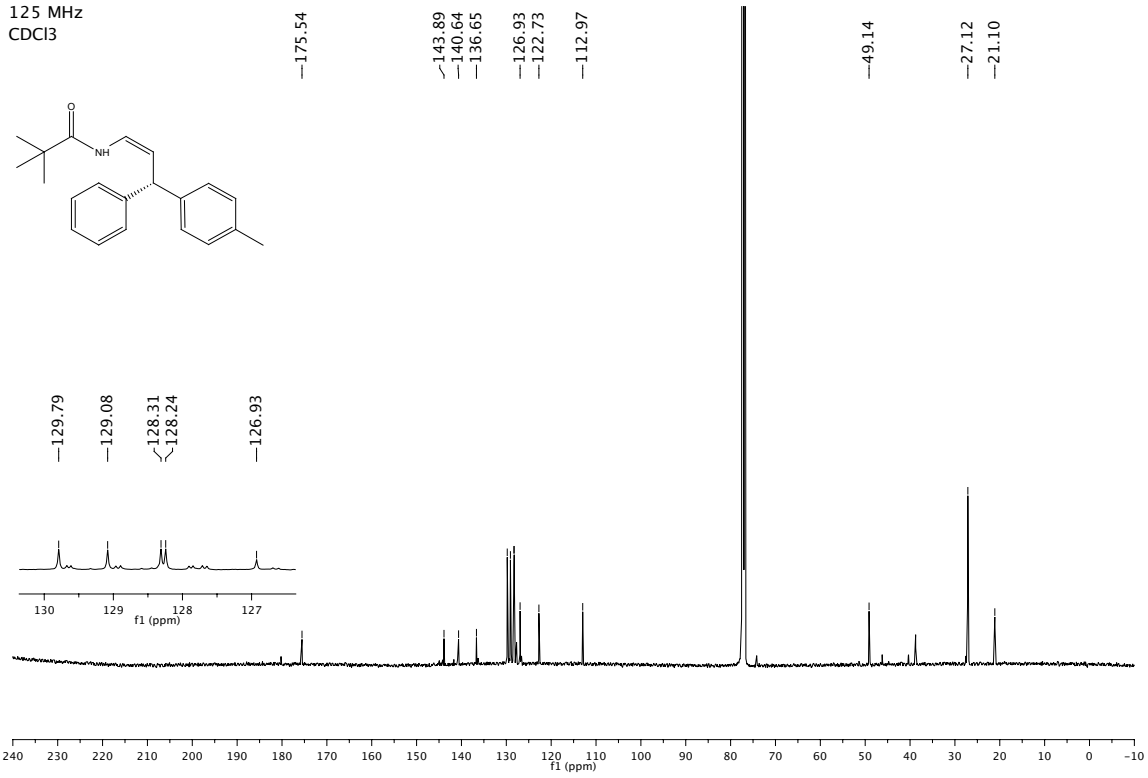
(S)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **403**





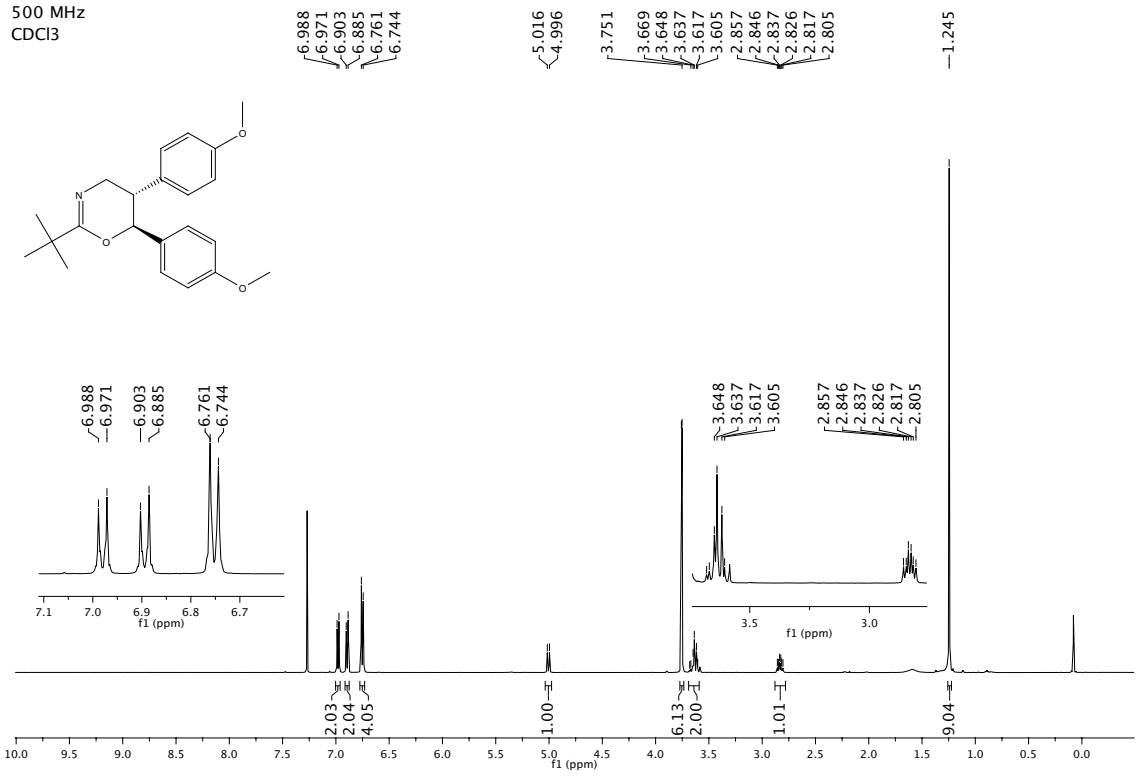
(S,Z)-N-(3-phenyl-3-(p-tolyl)prop-1-en-1-yl)pivalamide **407**

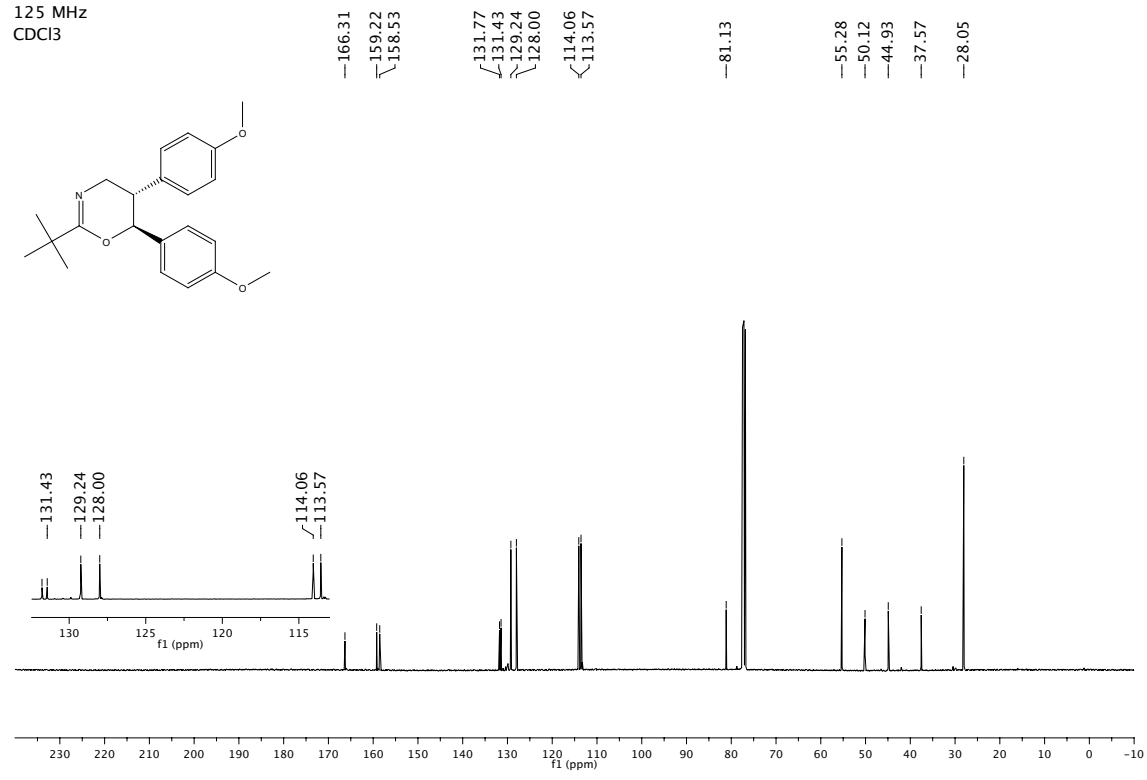




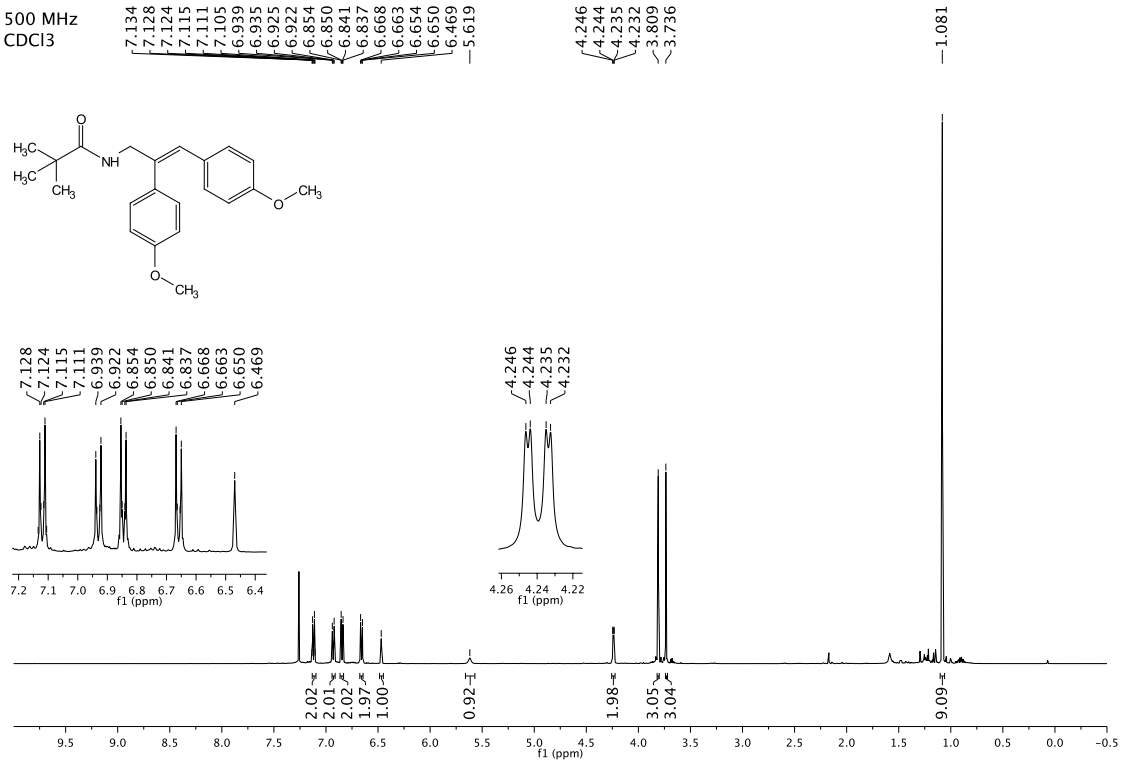
viii.1.3 Oxazine products

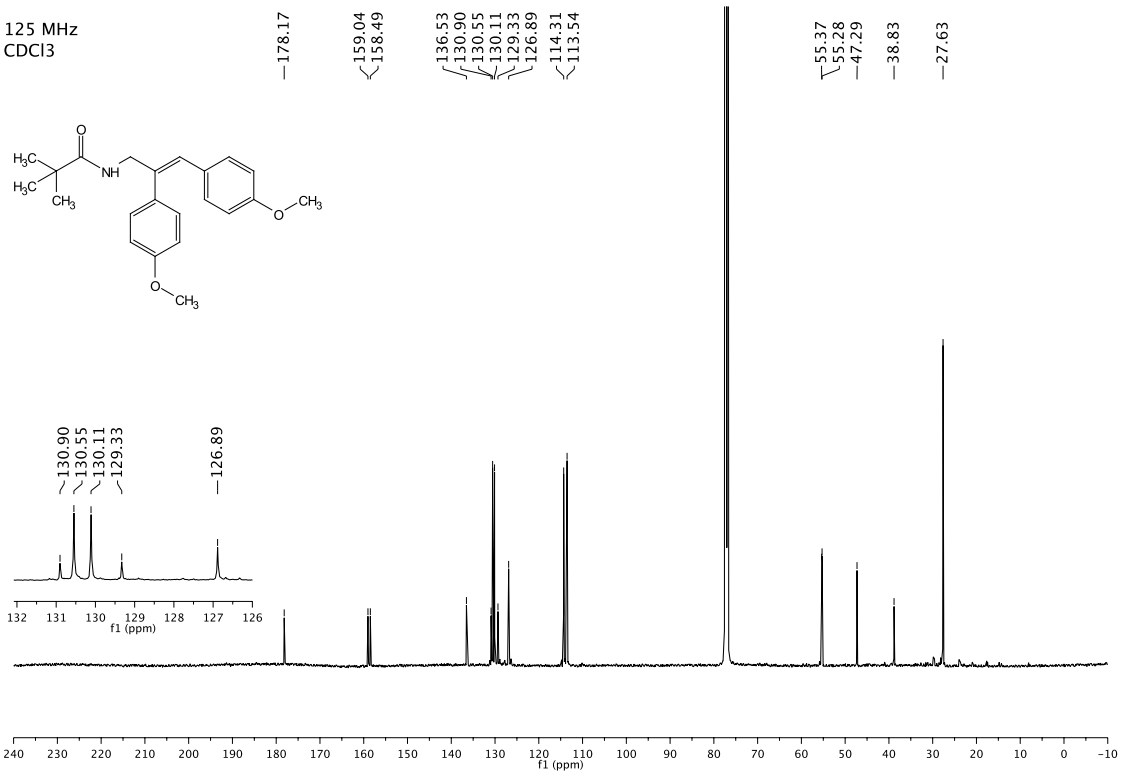
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **410**



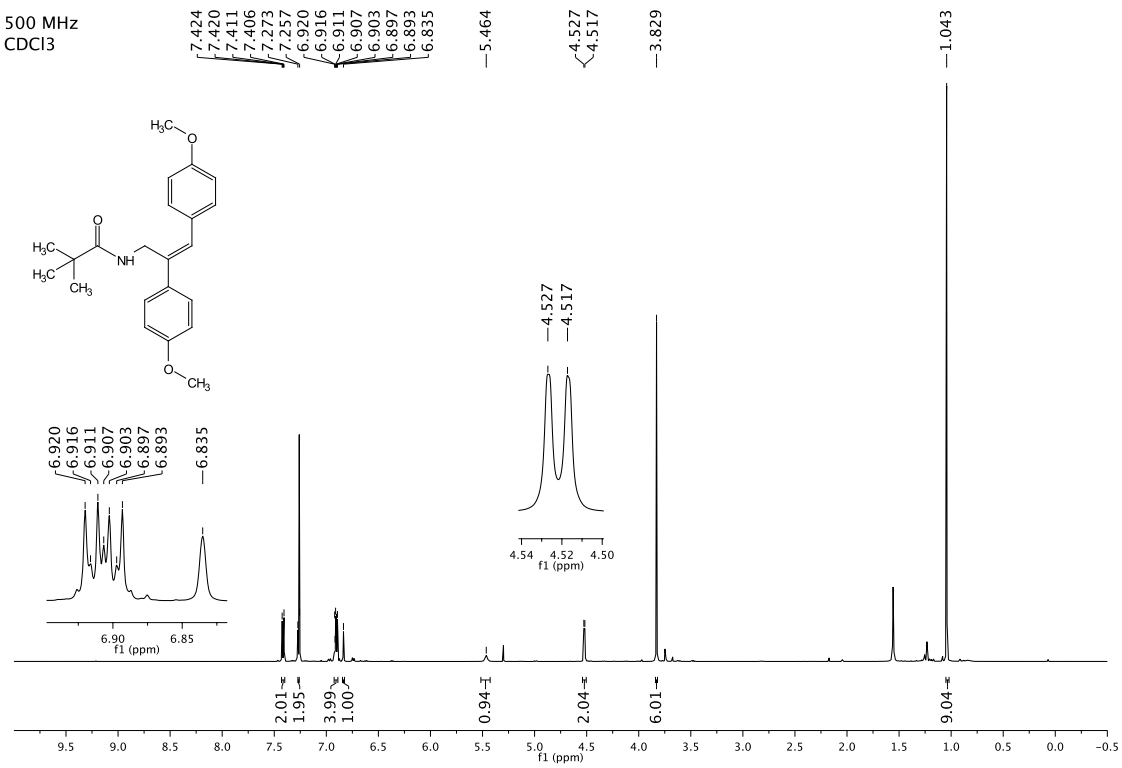


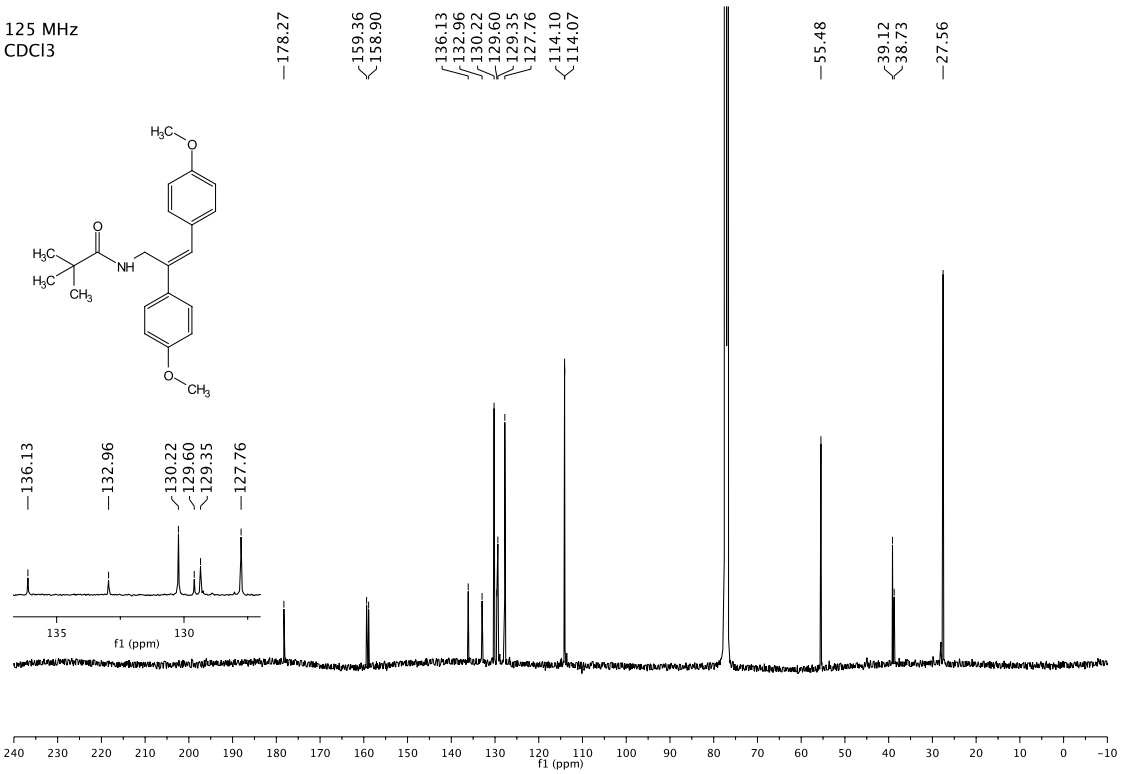
(E)-N-(2,3-bis(4-methoxyphenyl)allyl)pivalamide **413a**



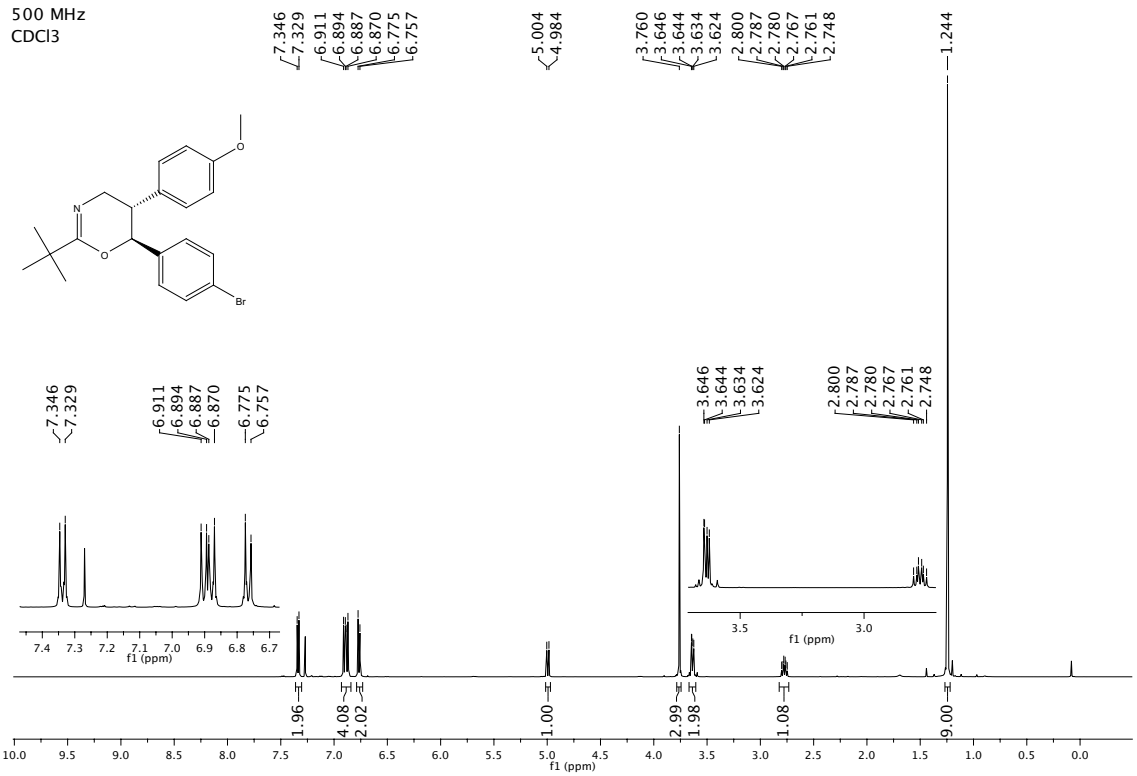


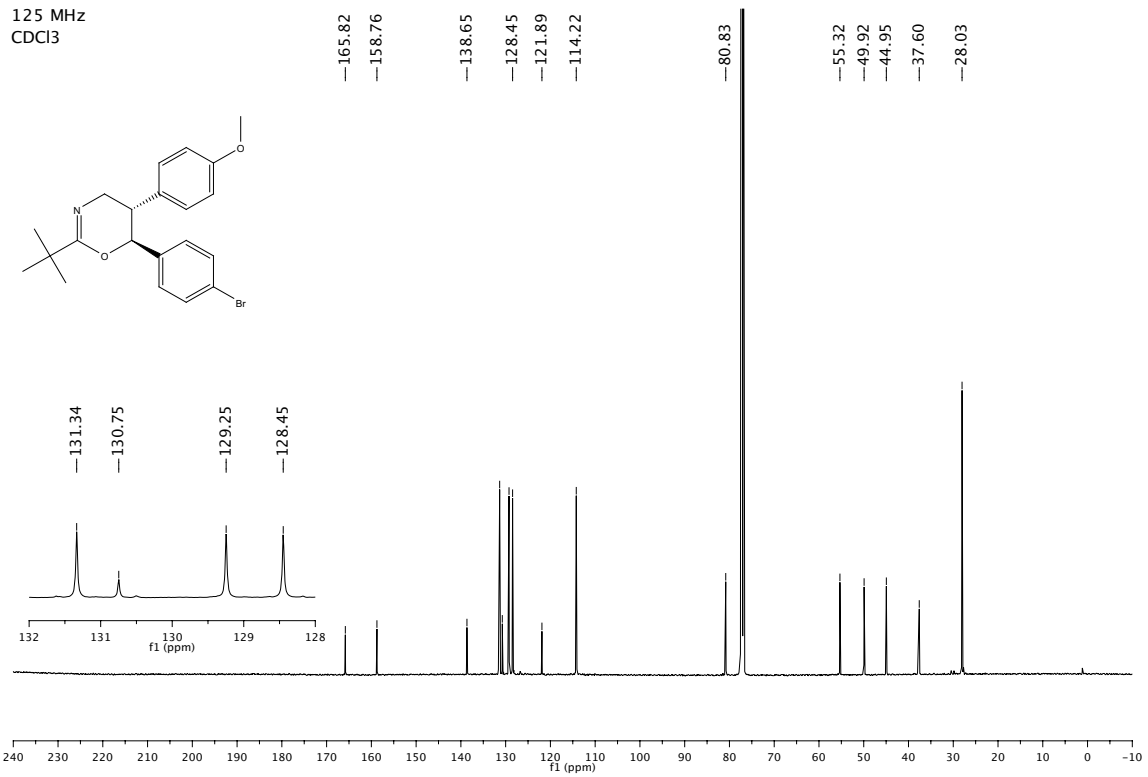
(Z)-N-(2,3-bis(4-methoxyphenyl)allyl)pivalamide **413b**



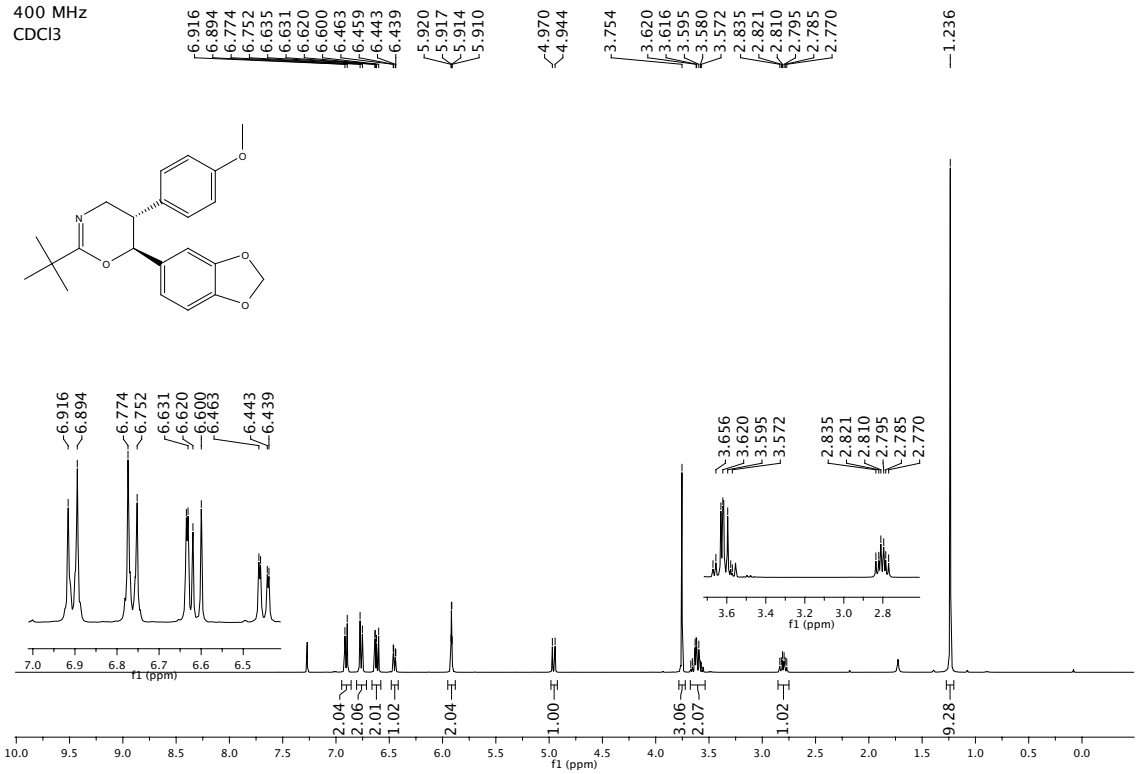


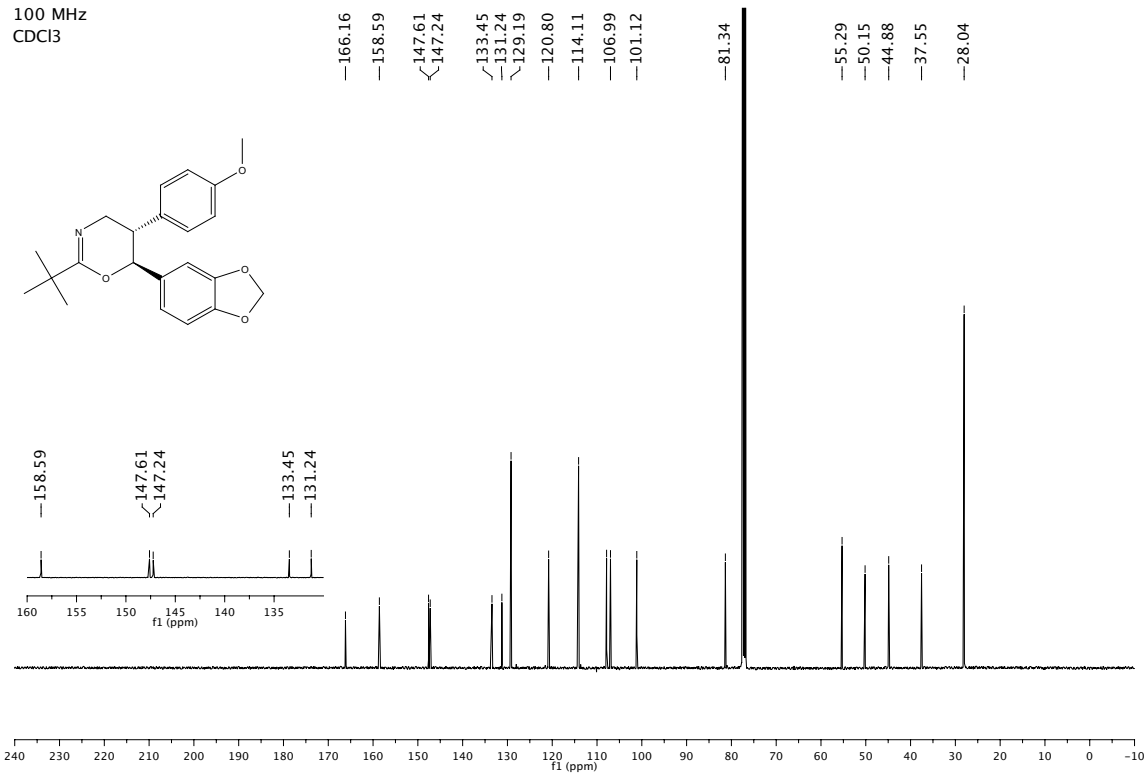
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-bromophenyl)-5,6-dihydro-4H-1,3-oxazine **412**



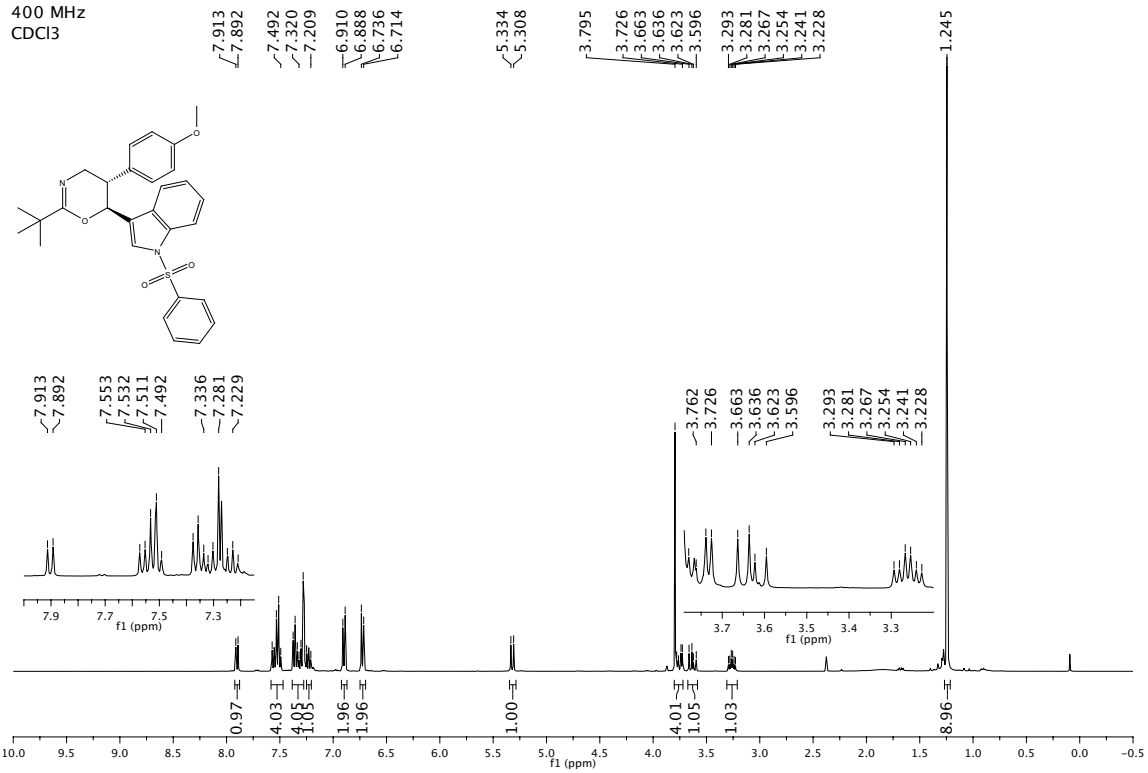


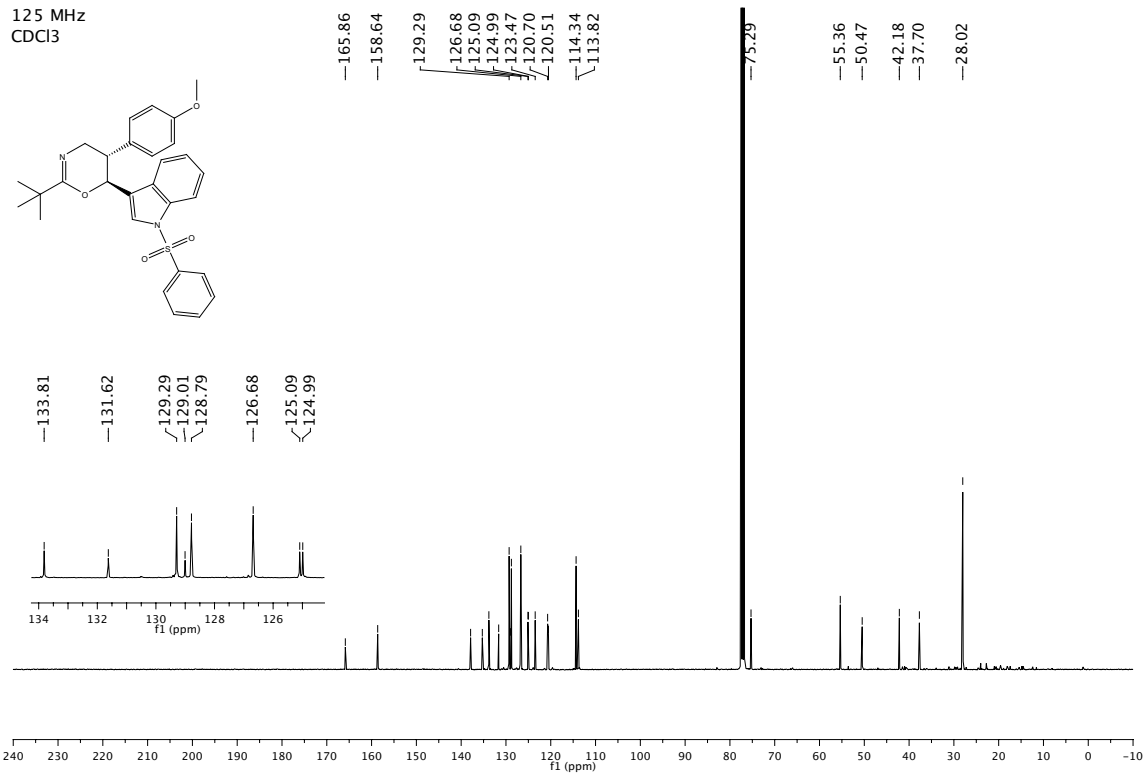
(5S,6S)-6-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butyl)-5-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **414**



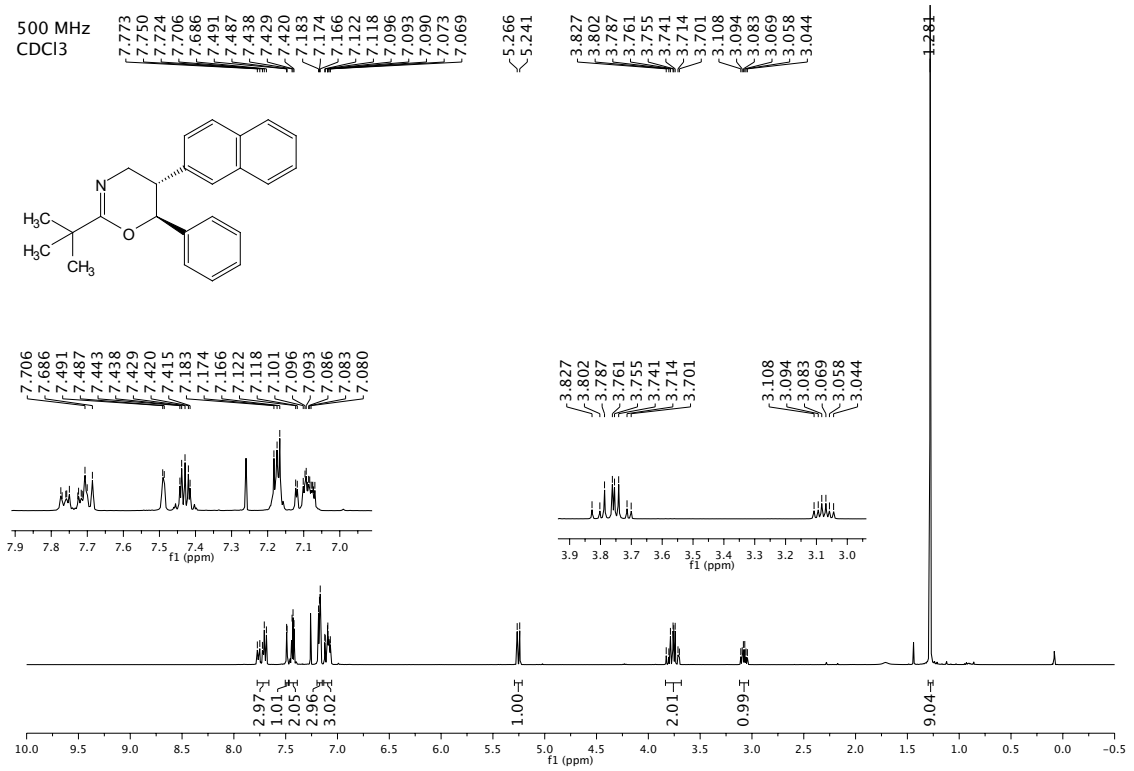


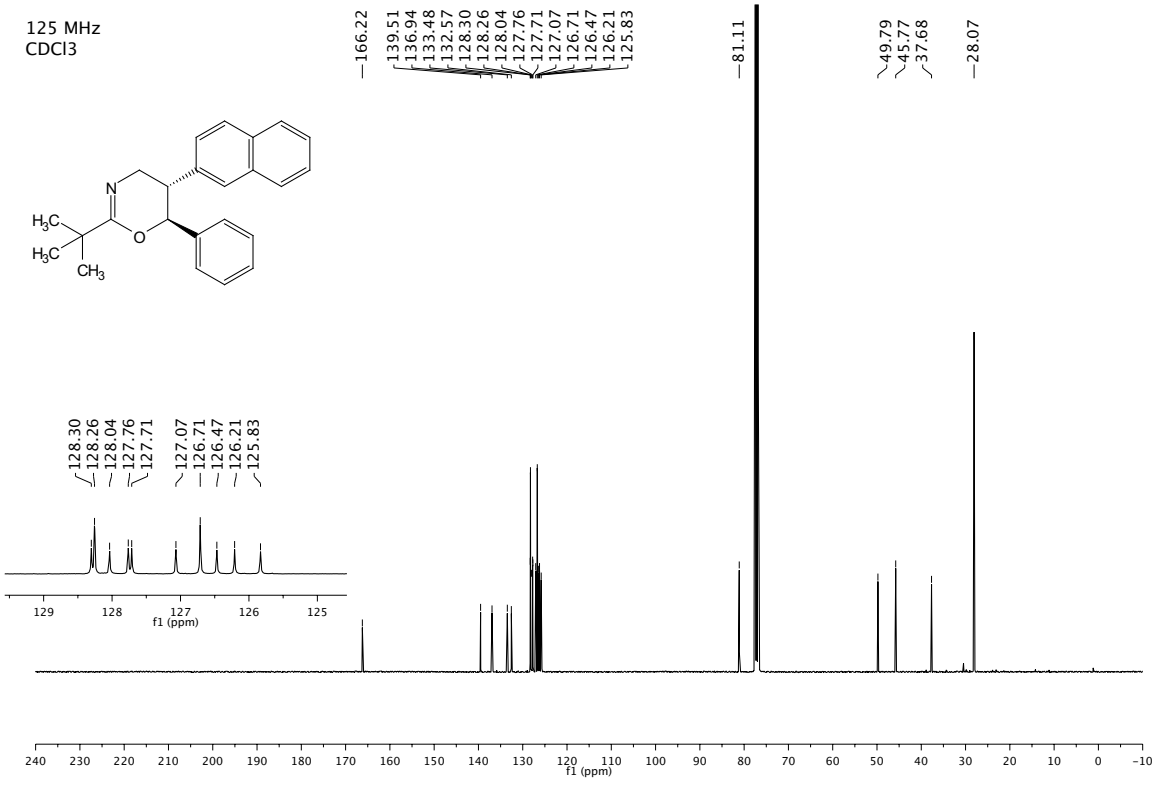
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(1-(phenylsulfonyl)-1H-indol-3-yl)-5,6-dihydro-4H-1,3-oxazine **415**



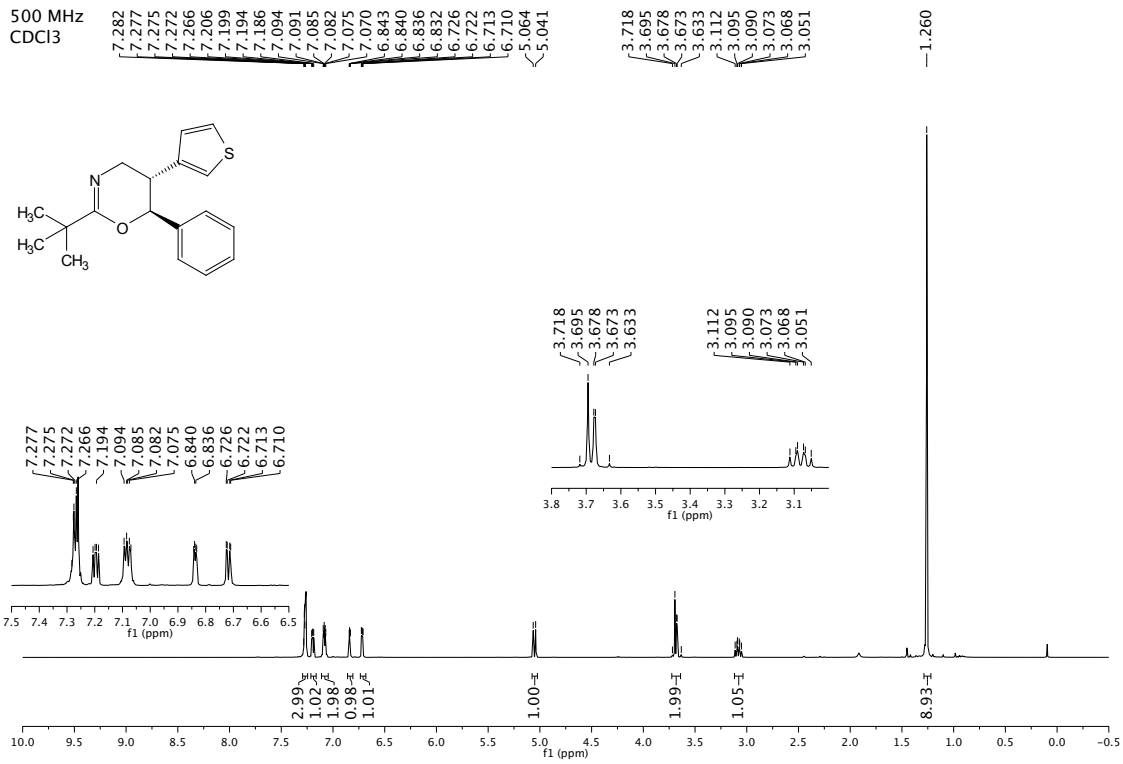


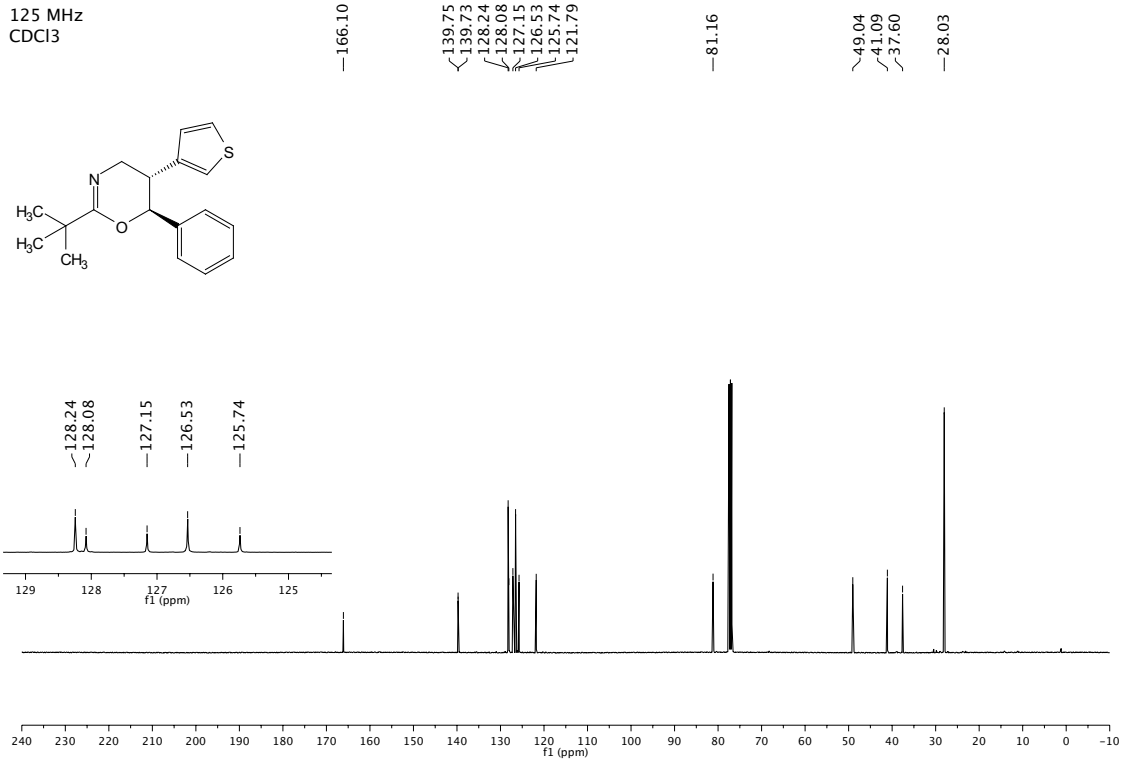
(5S,6S)-2-(tert-butyl)-5-(naphthalen-2-yl)-6-phenyl-5,6-dihydro-4H-1,3-oxazine **423**



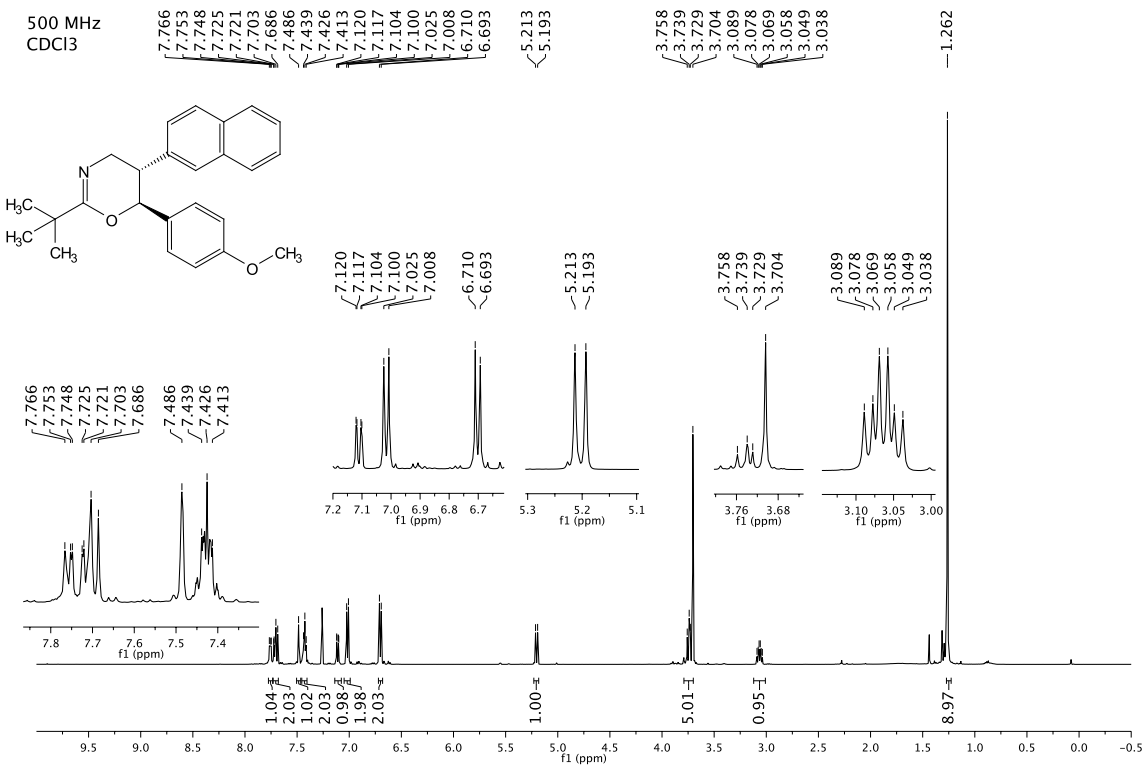


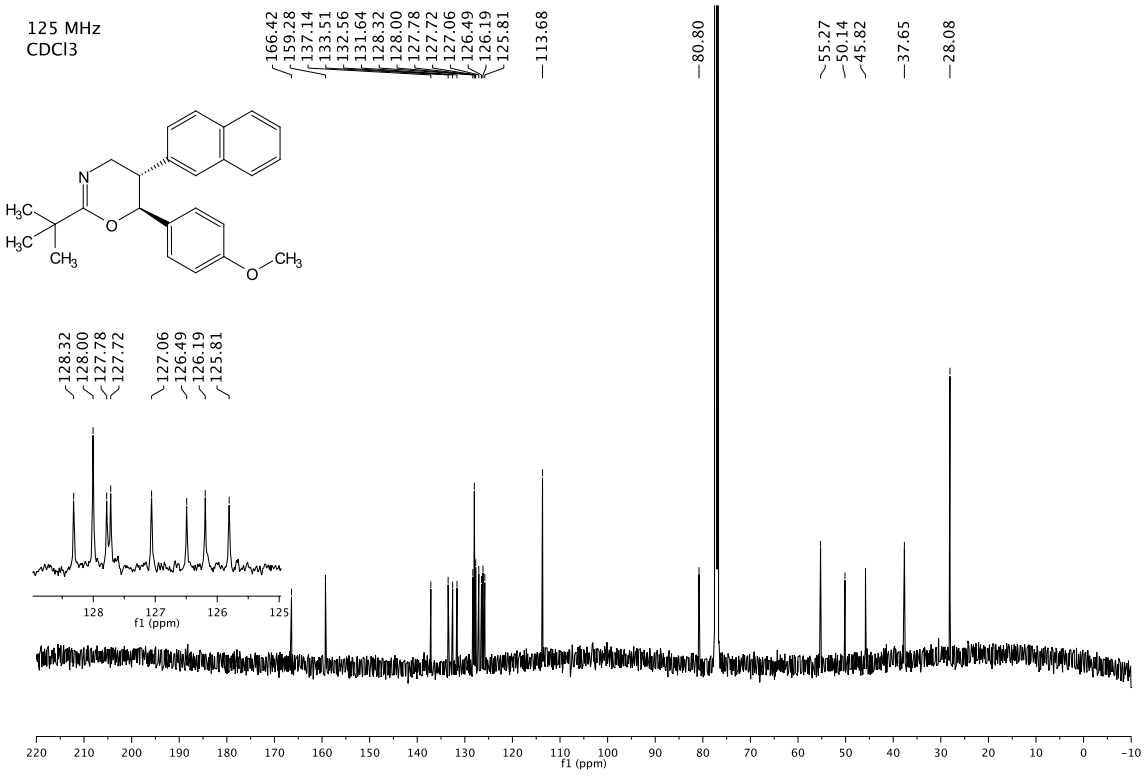
(5S,6S)-2-(tert-butyl)-6-phenyl-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **424**



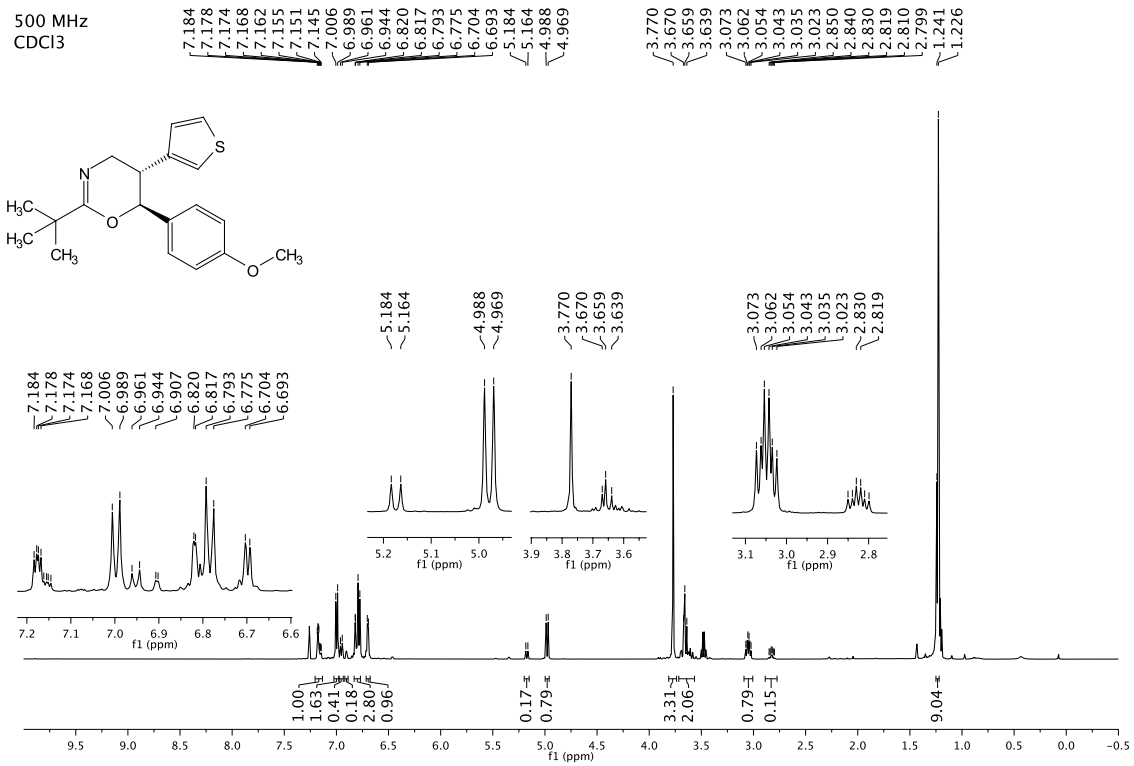


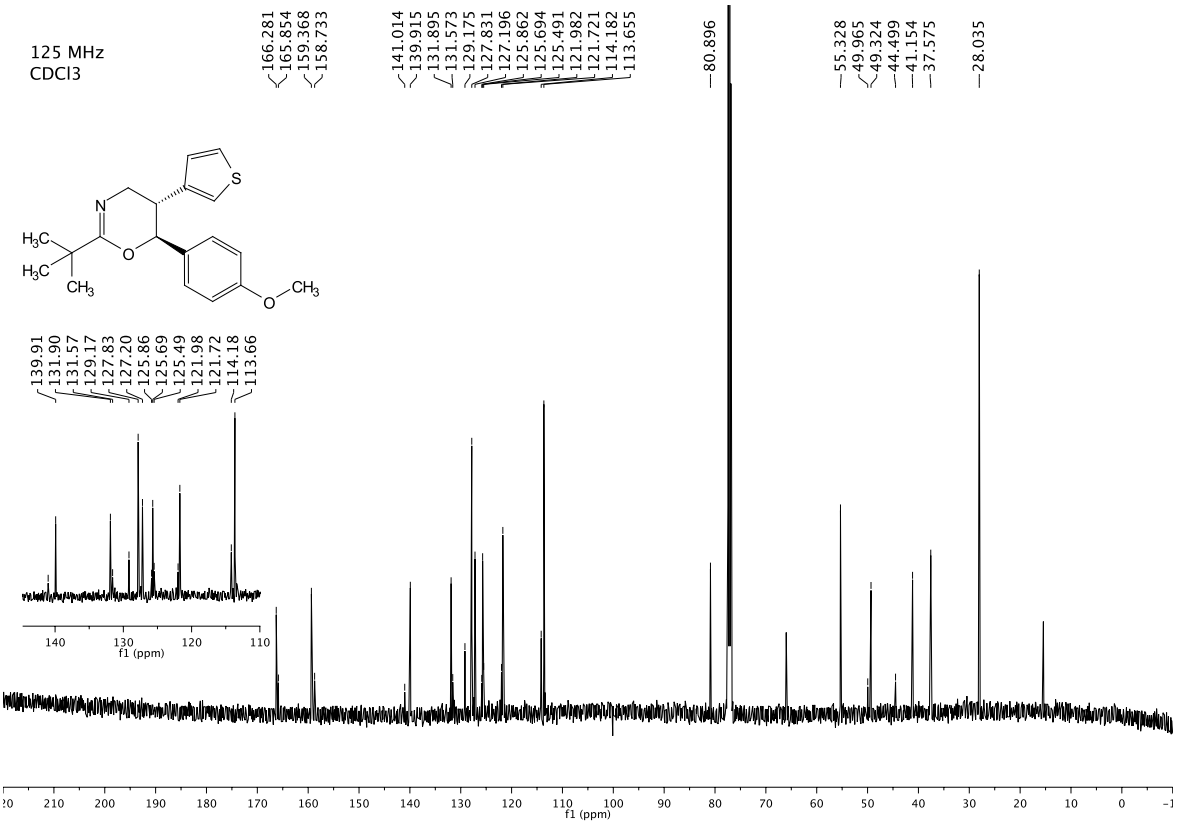
(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(naphthalen-2-yl)-5,6-dihydro-4H-1,3-oxazine **425**





(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **426**

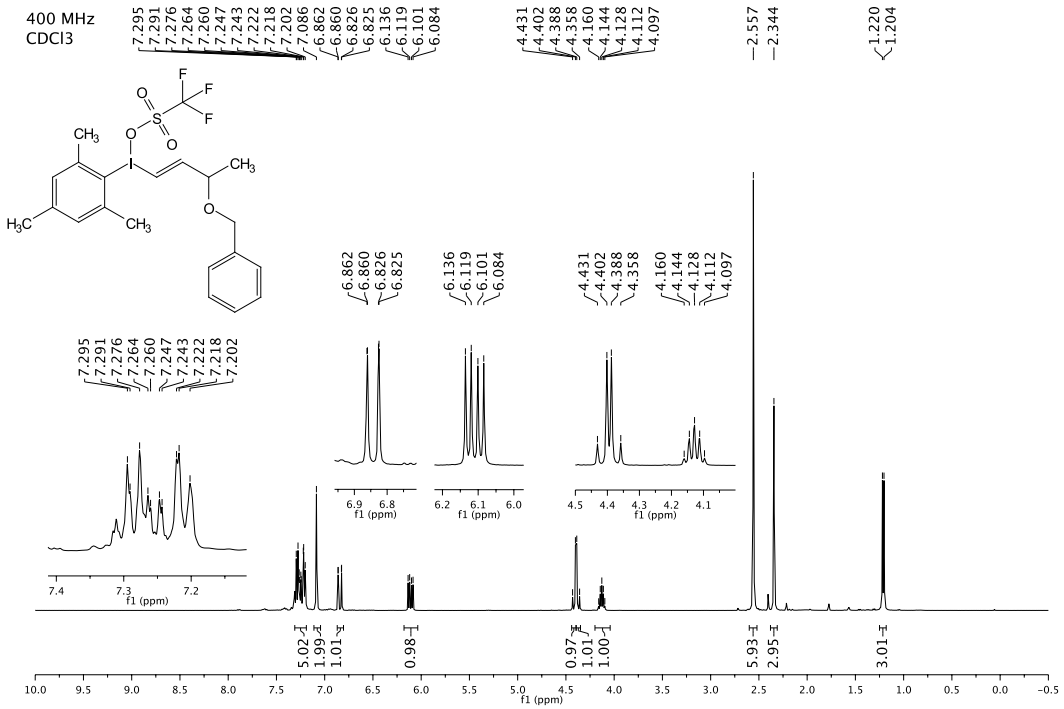


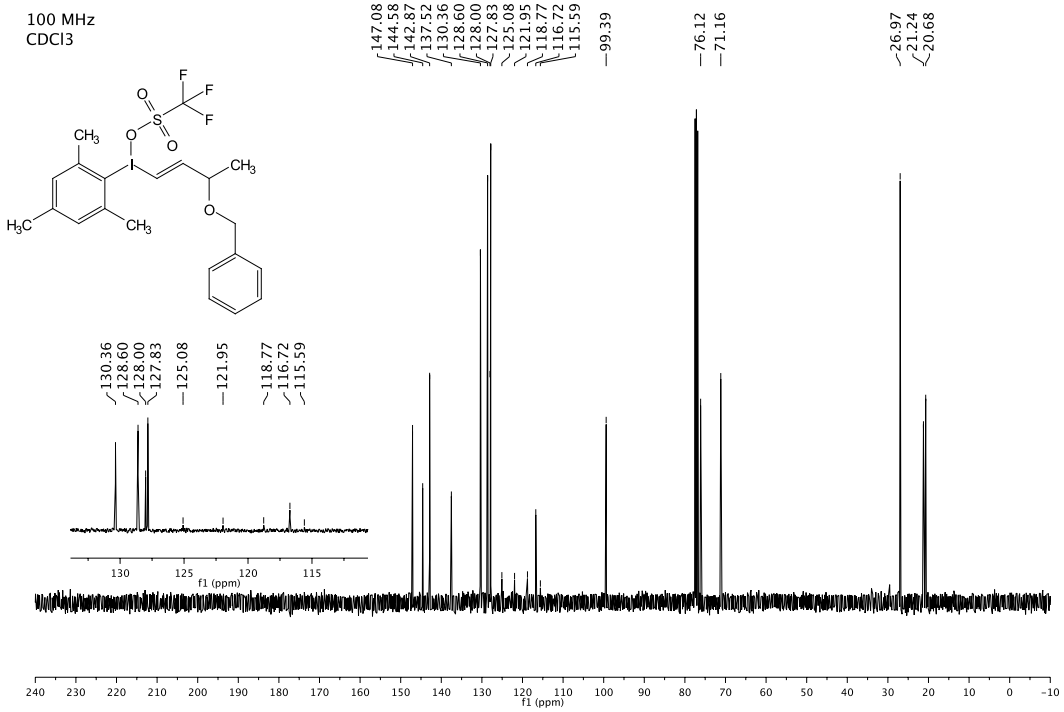


viii.2 Studies Towards the Total Synthesis of (−)-Lyngbyaloside B

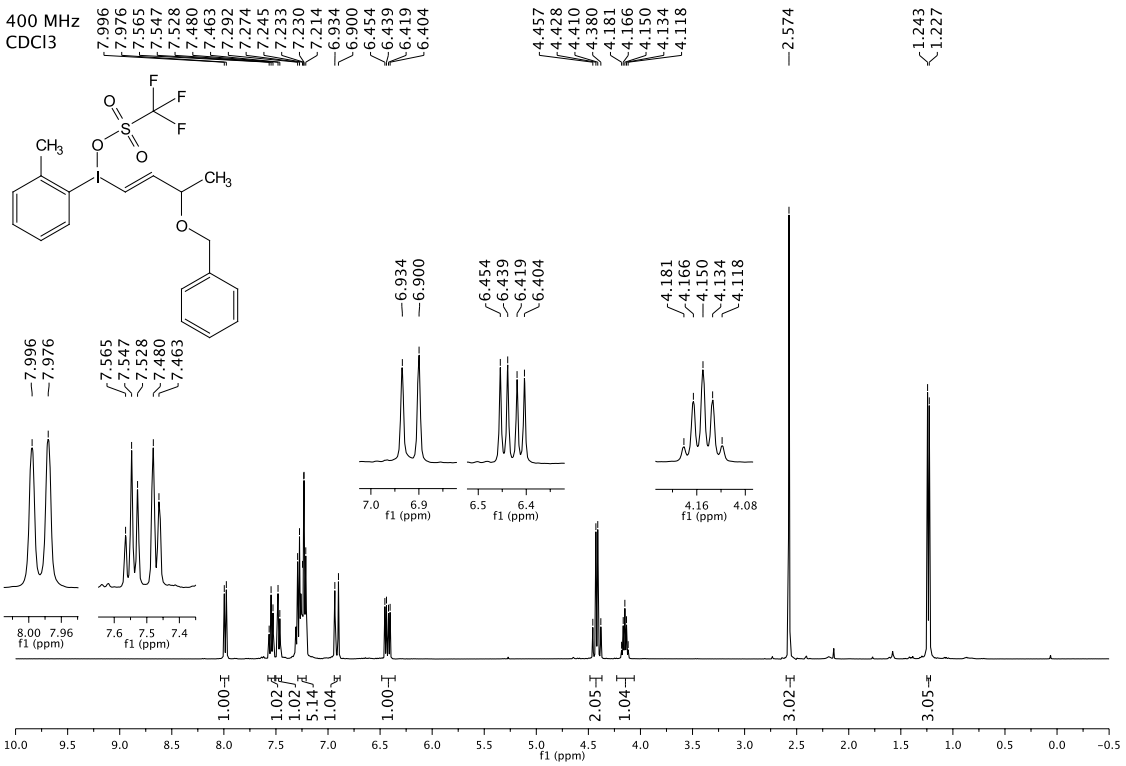
viii.2.1 Model coupling

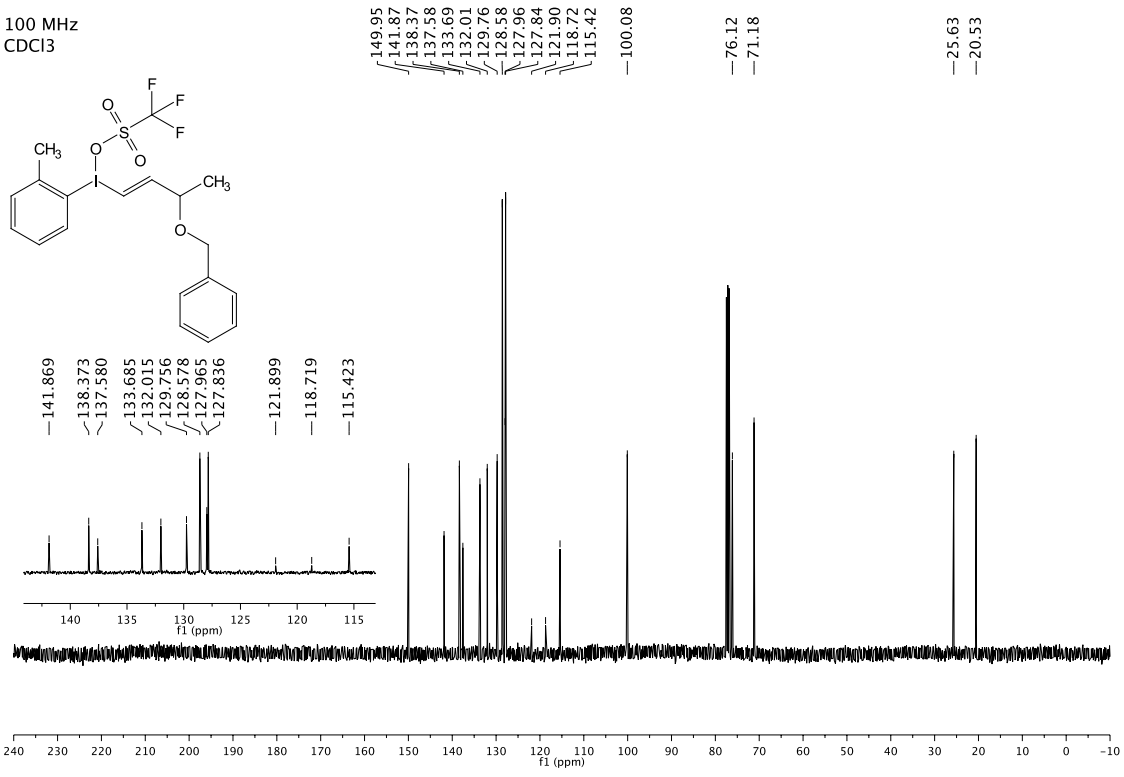
(E)-(3-(benzyloxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate **481**



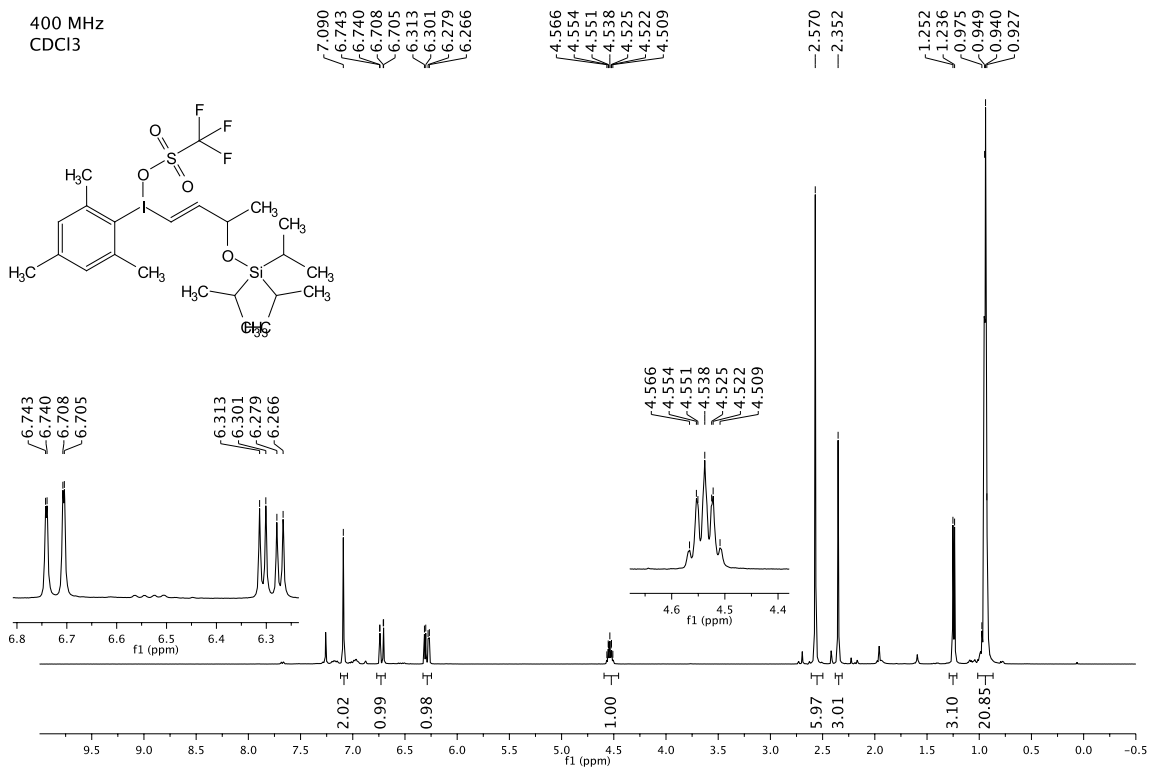


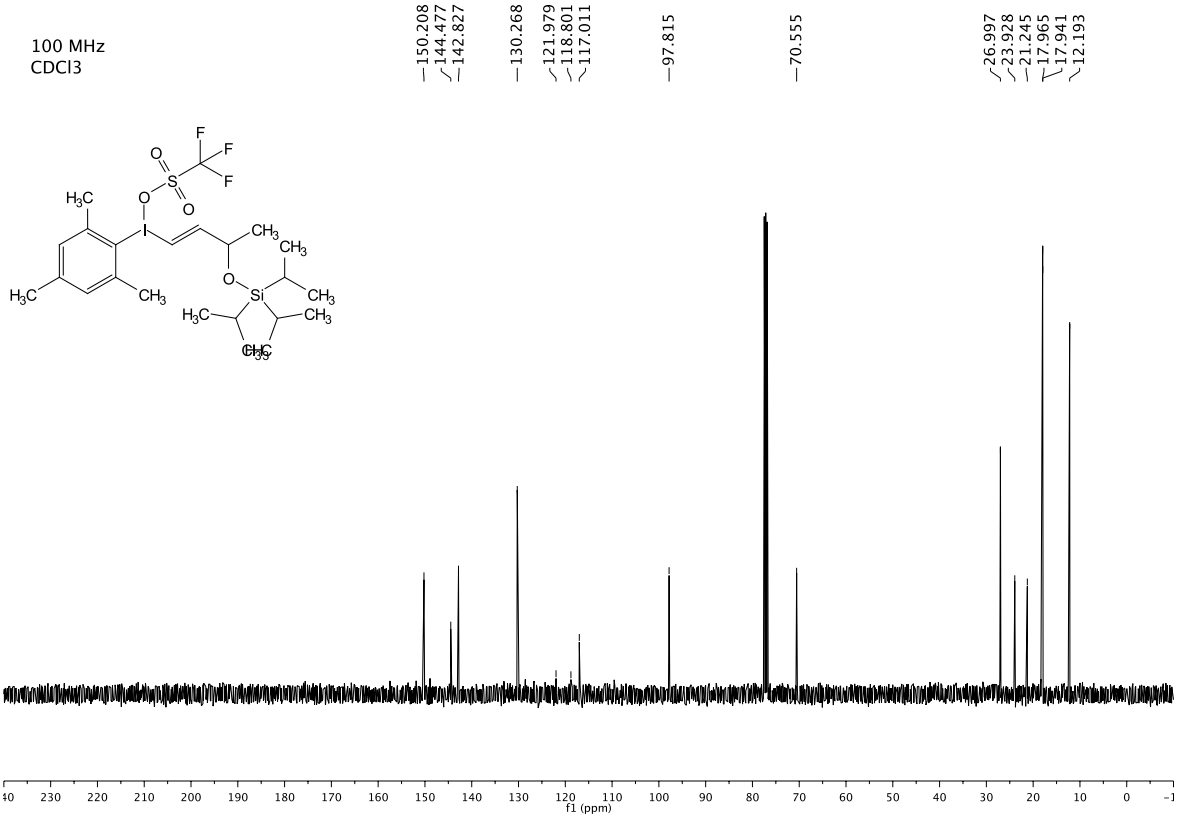
(E)-(3-(benzyloxy)but-1-en-1-yl)(o-tolyl)iodonium trifluoromethanesulfonate **482**



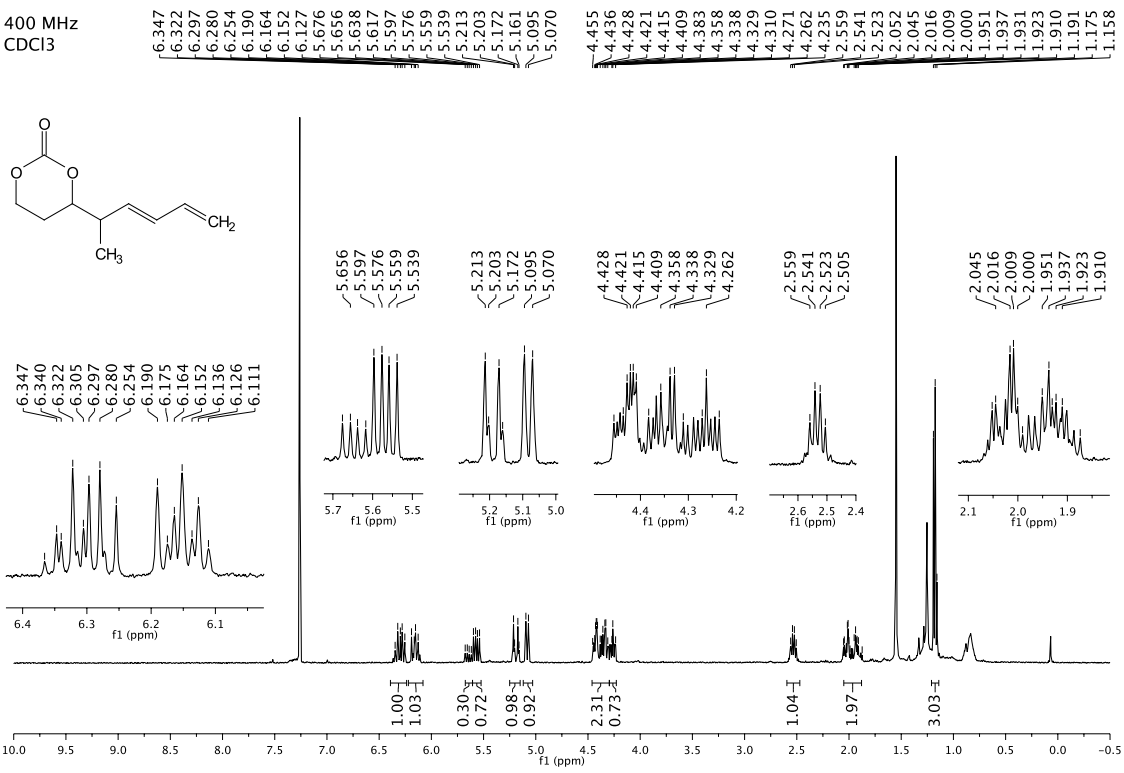


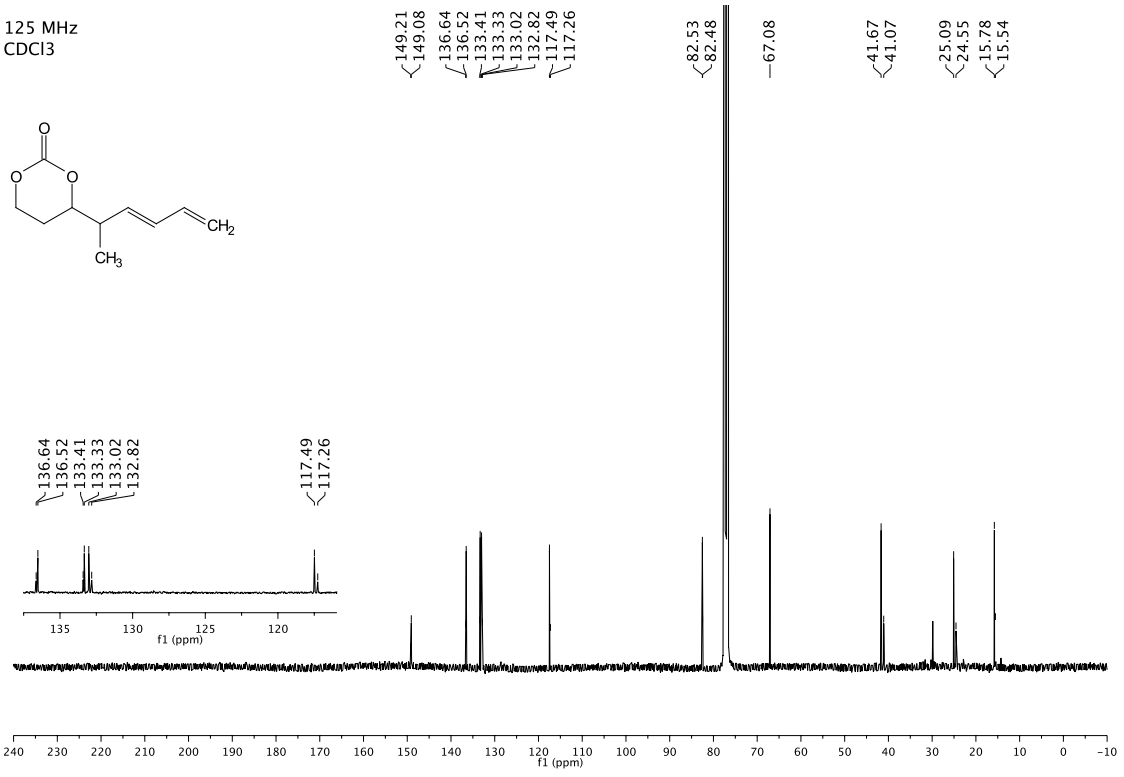
(E)-(3-((triisopropylsilyl)oxy)but-1-en-1-yl)(mesityl)iodonium trifluoromethanesulfonate **483**



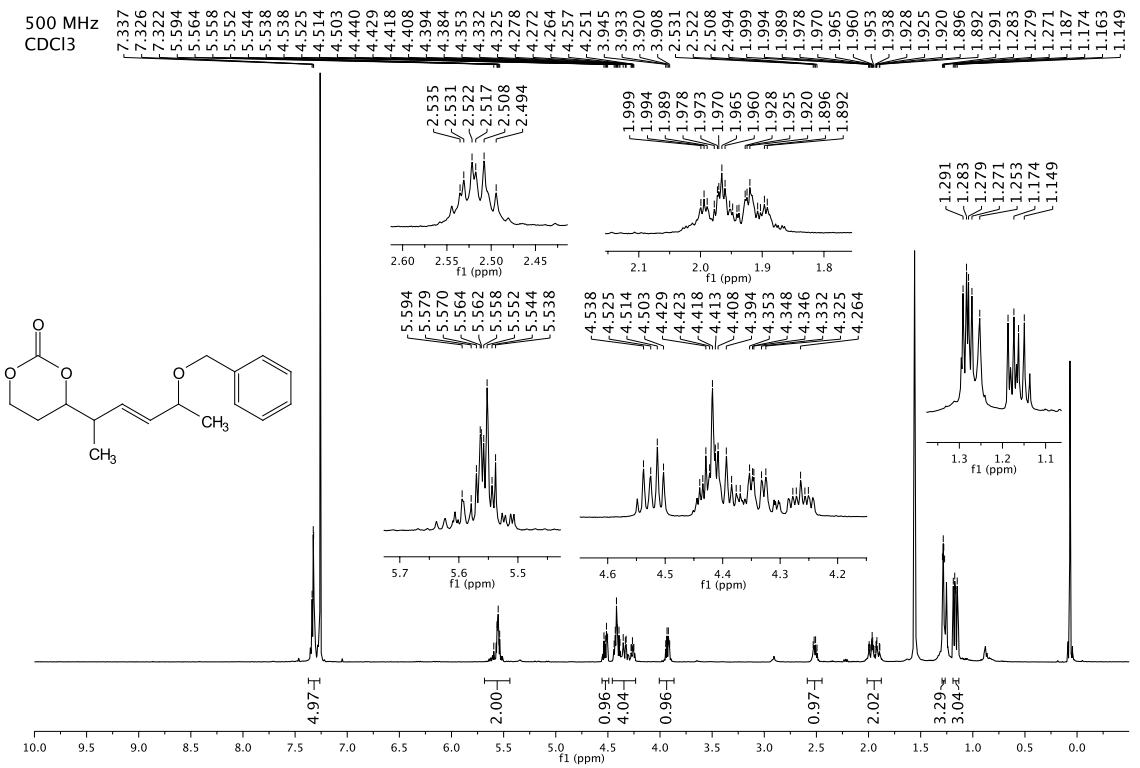


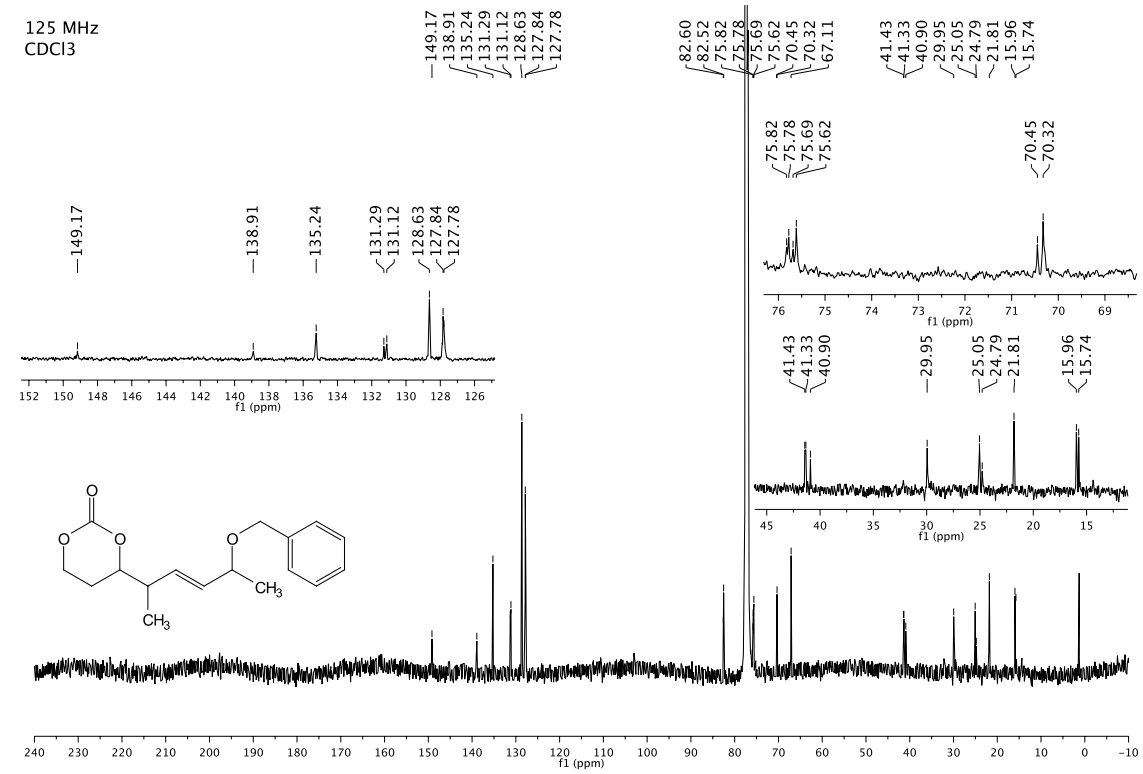
(E)-4-(hexa-3,5-dien-2-yl)-1,3-dioxan-2-one **484**





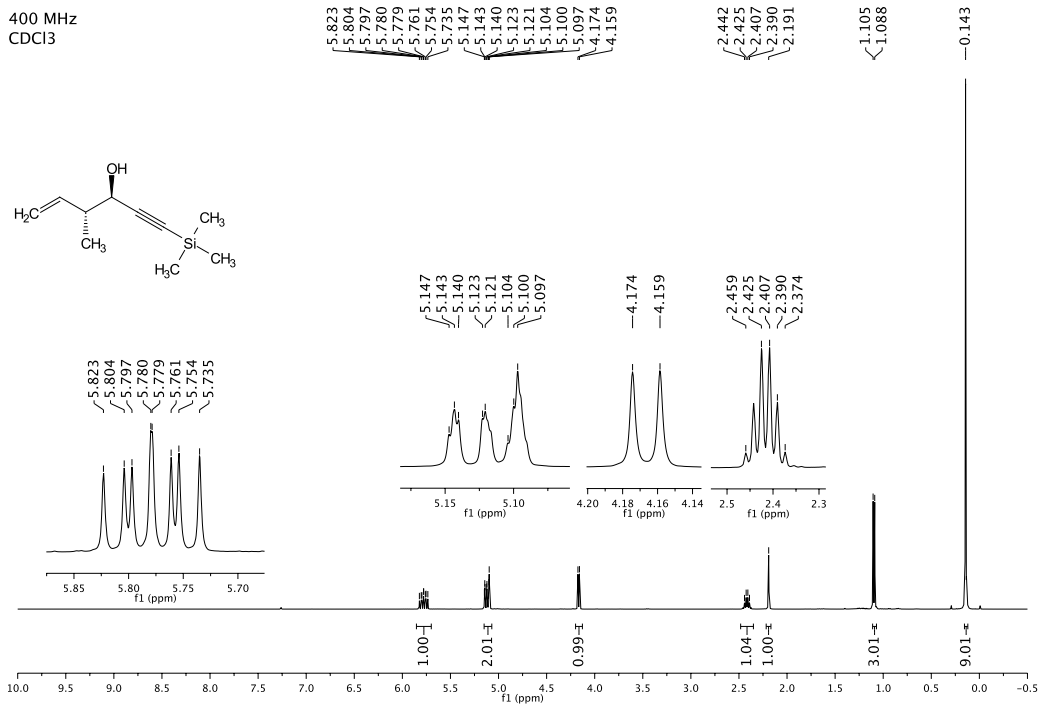
(E)-4-(5-(benzyloxy)hex-3-en-2-yl)-1,3-dioxan-2-one **478**

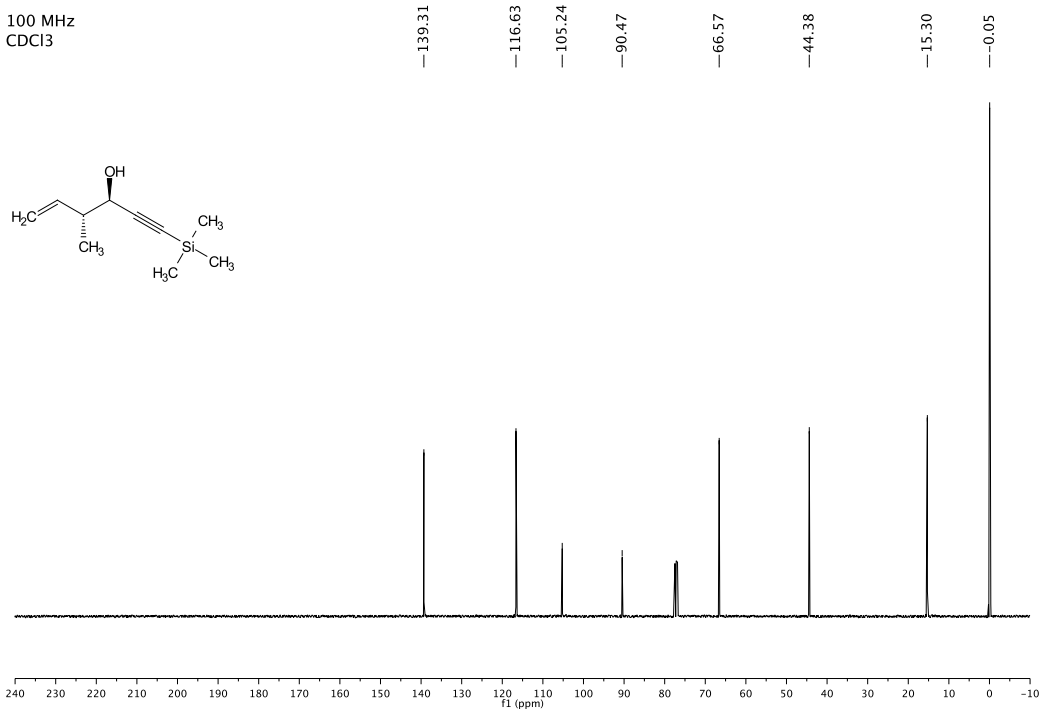




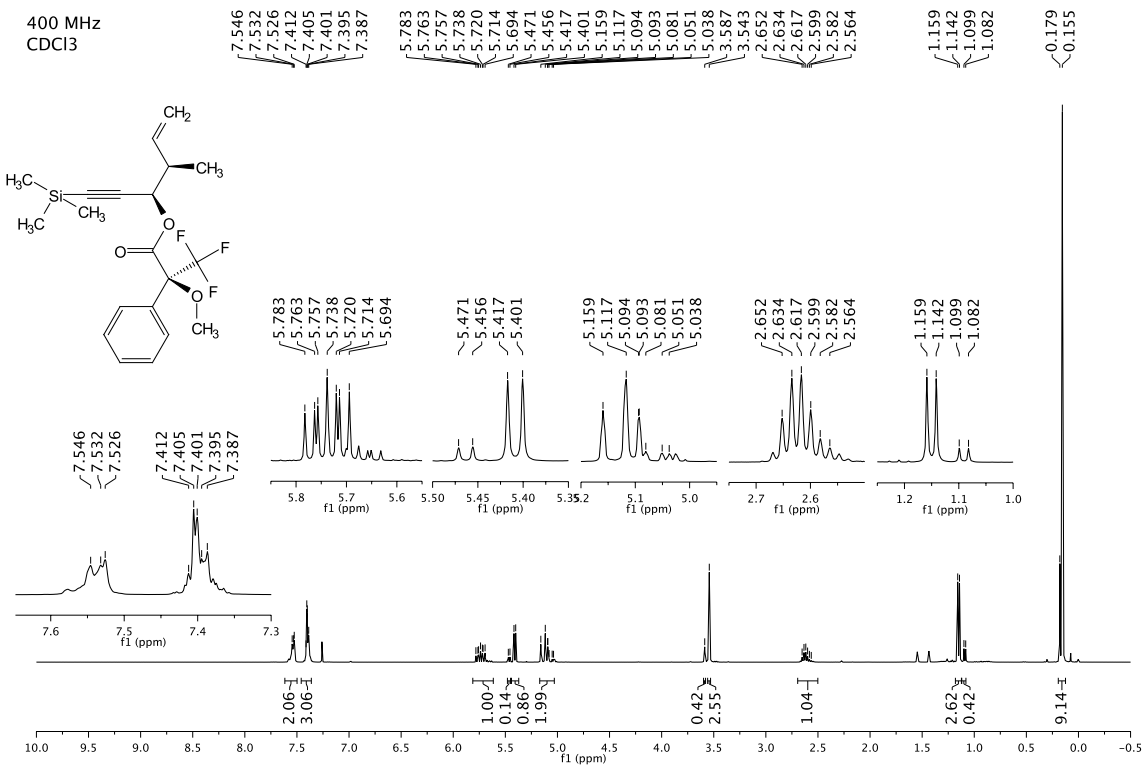
viii.2.2 First generation

(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol **511**

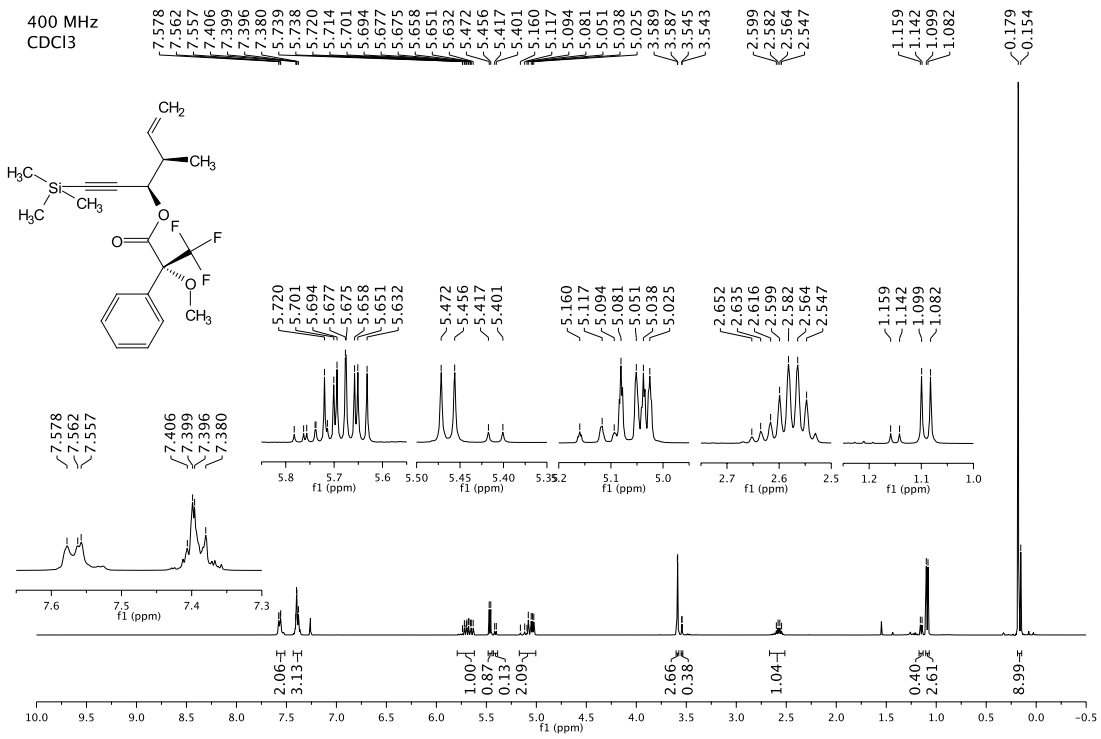




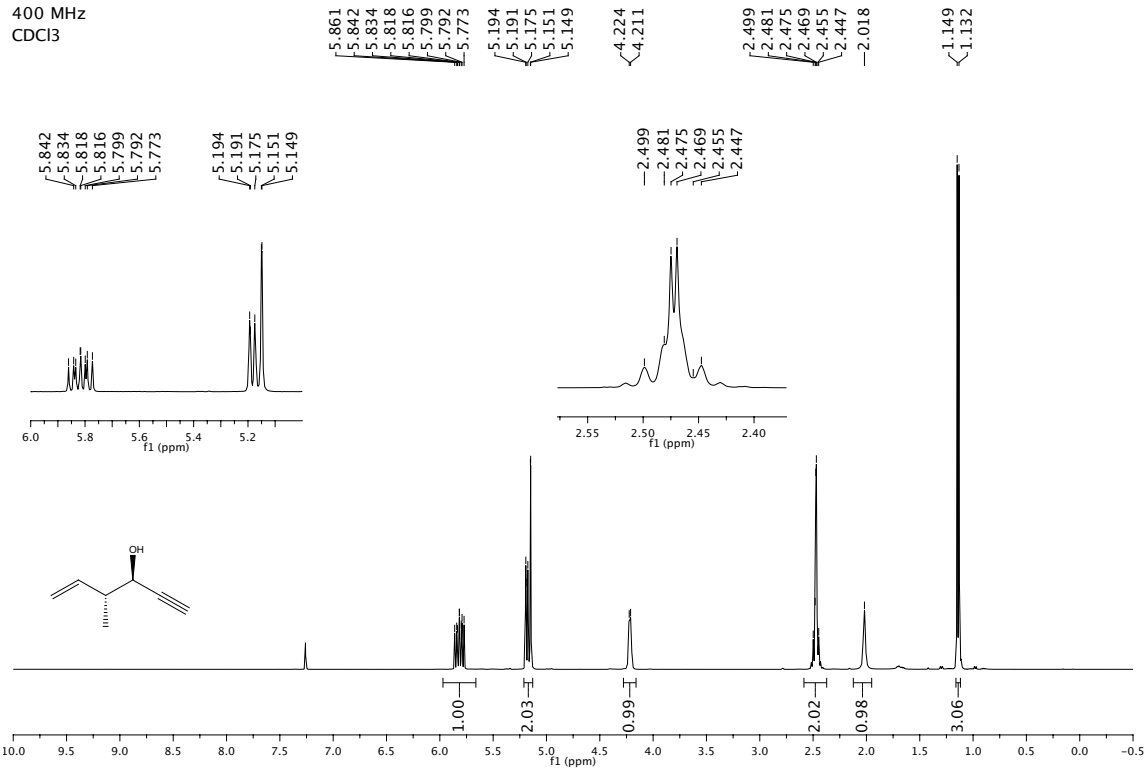
(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **511a**

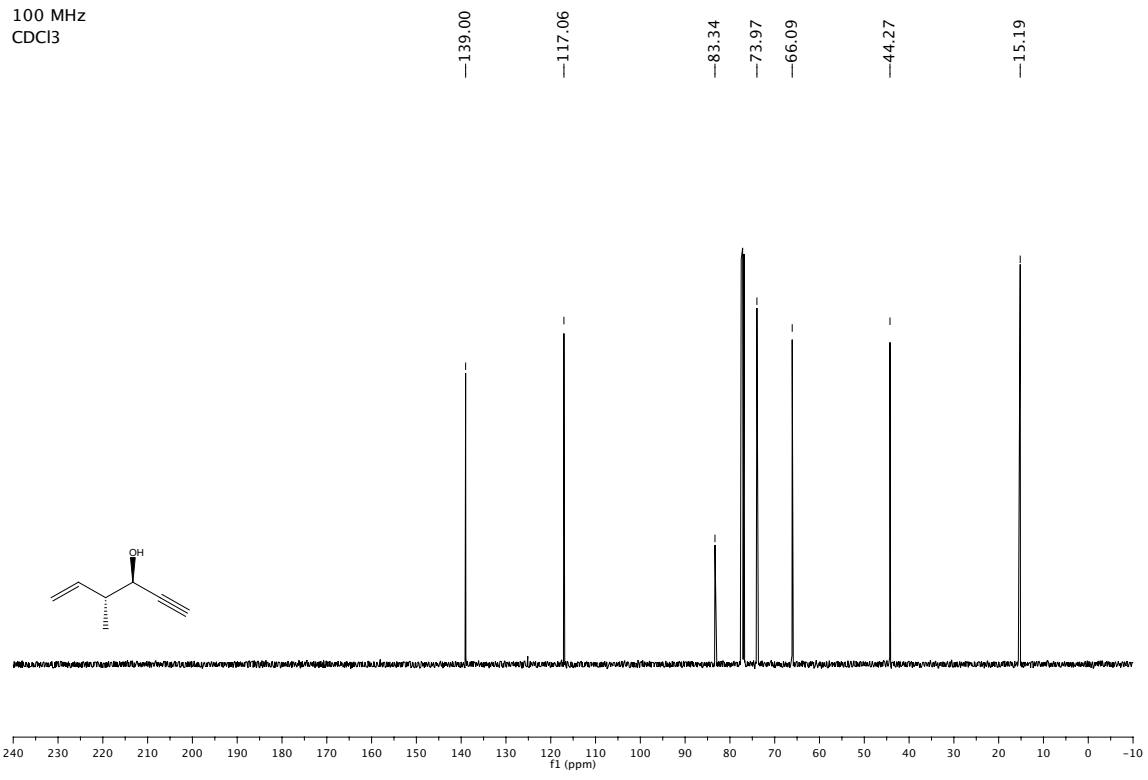


(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **511b**

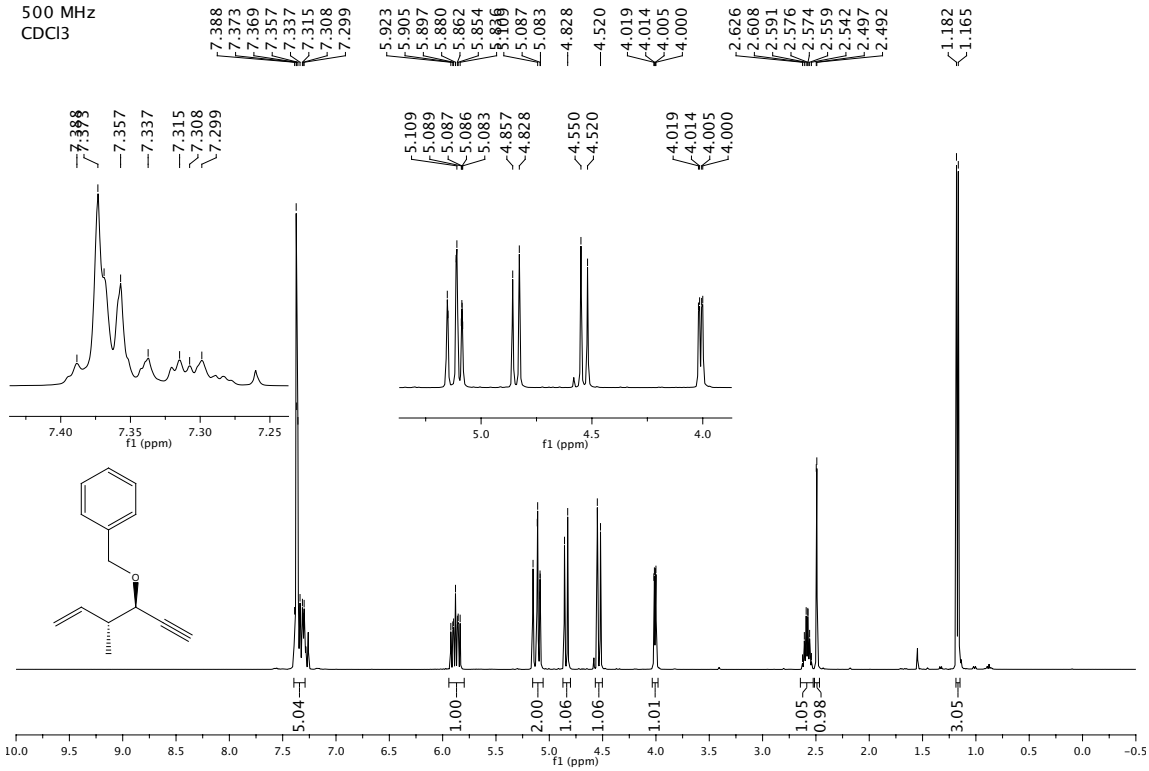


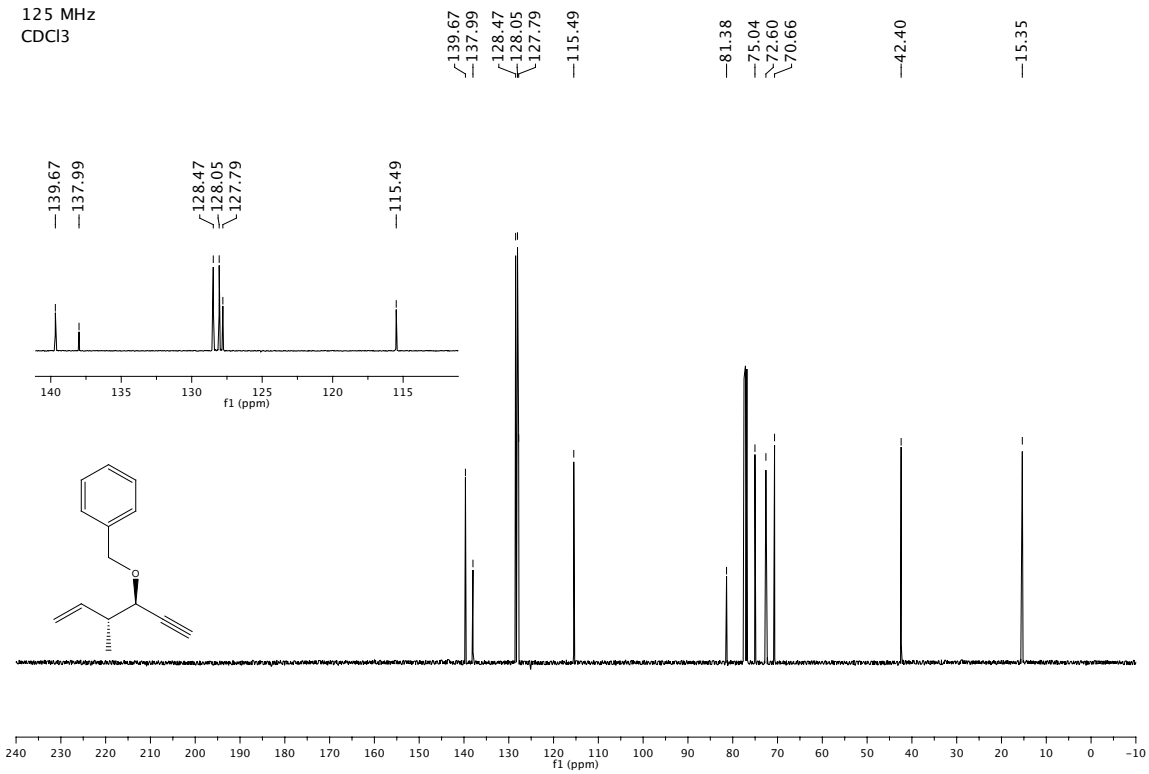
(3R,4R)-4-methylhex-5-en-1-yn-3-ol **514**



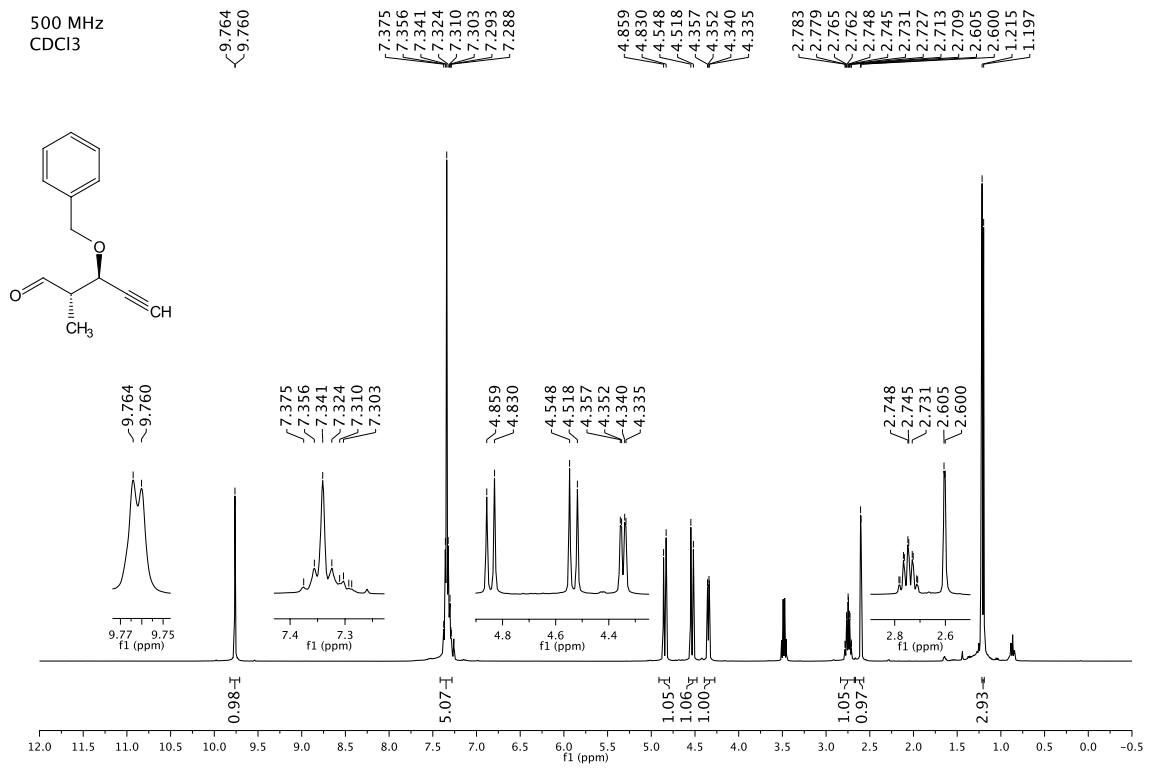


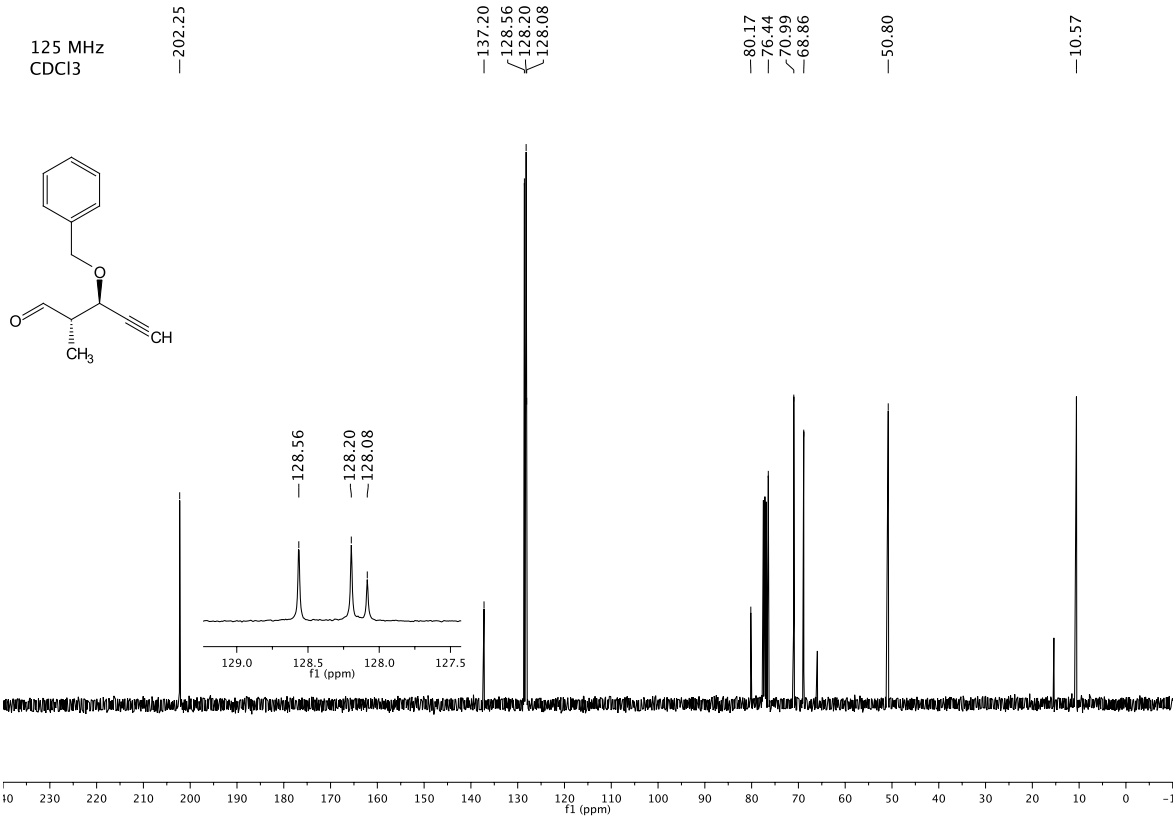
((((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)methyl)benzene **517**



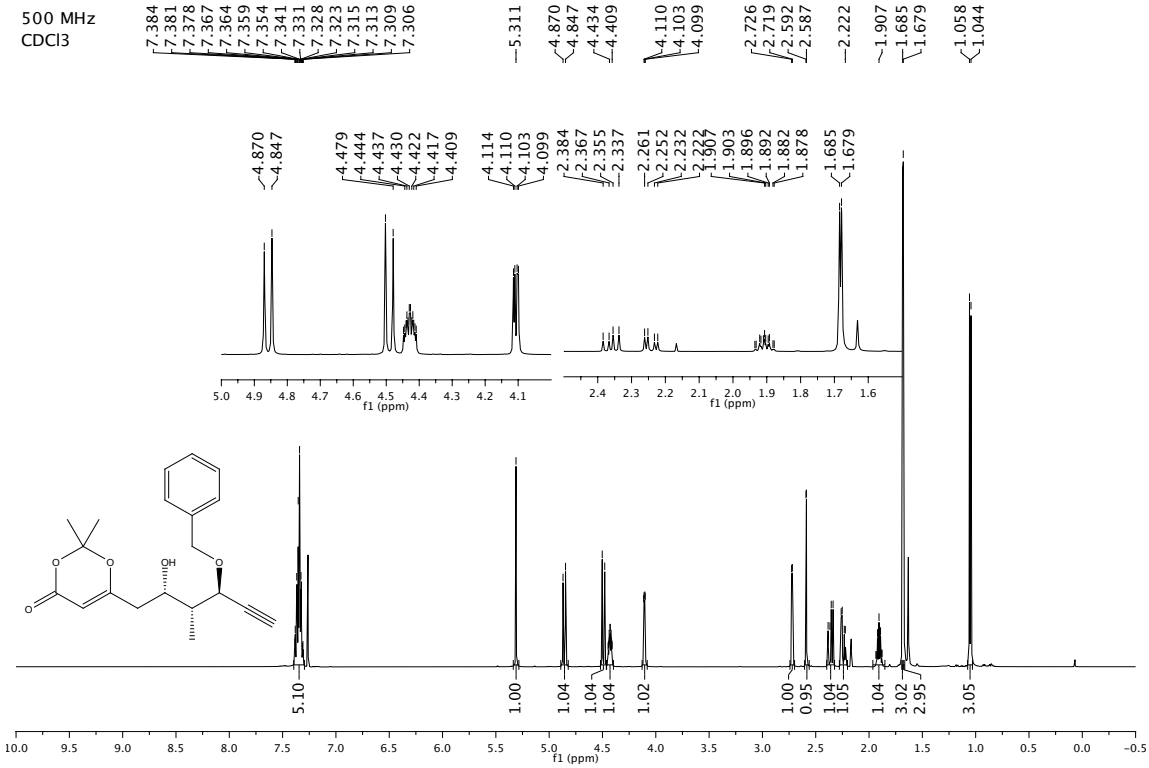


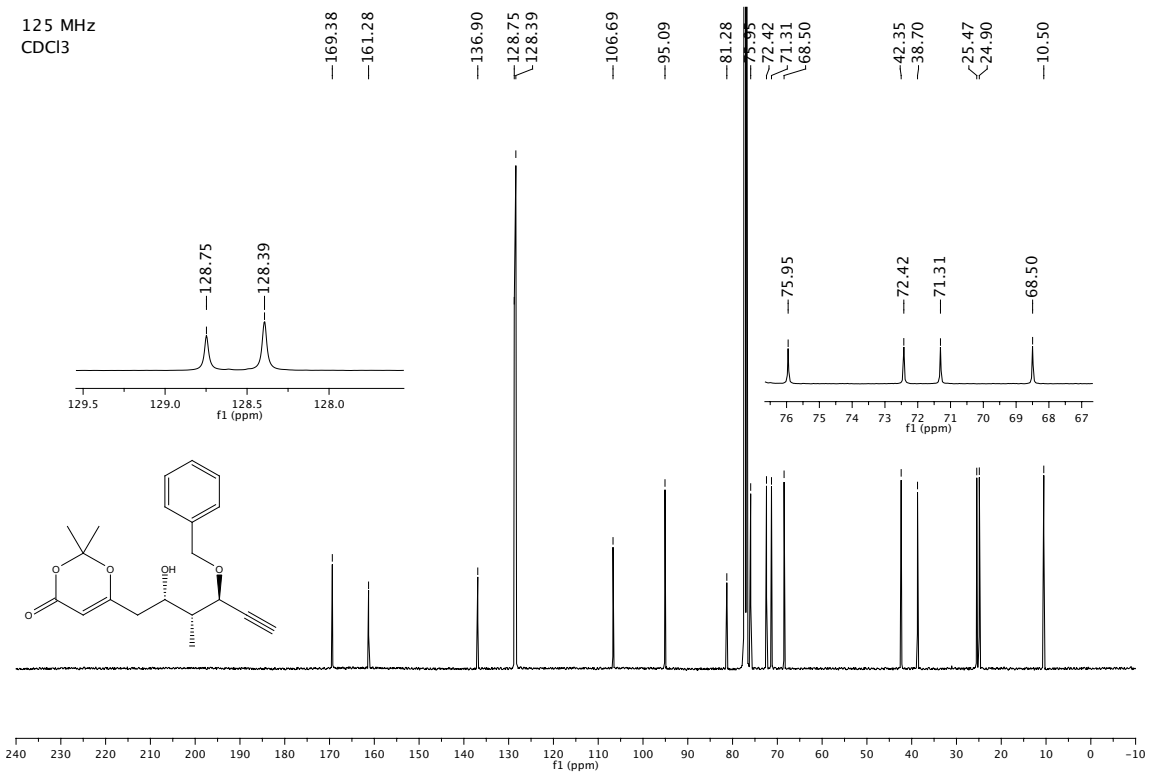
(2S,3R)-3-(benzyloxy)-2-methylpent-4-ynal **518**



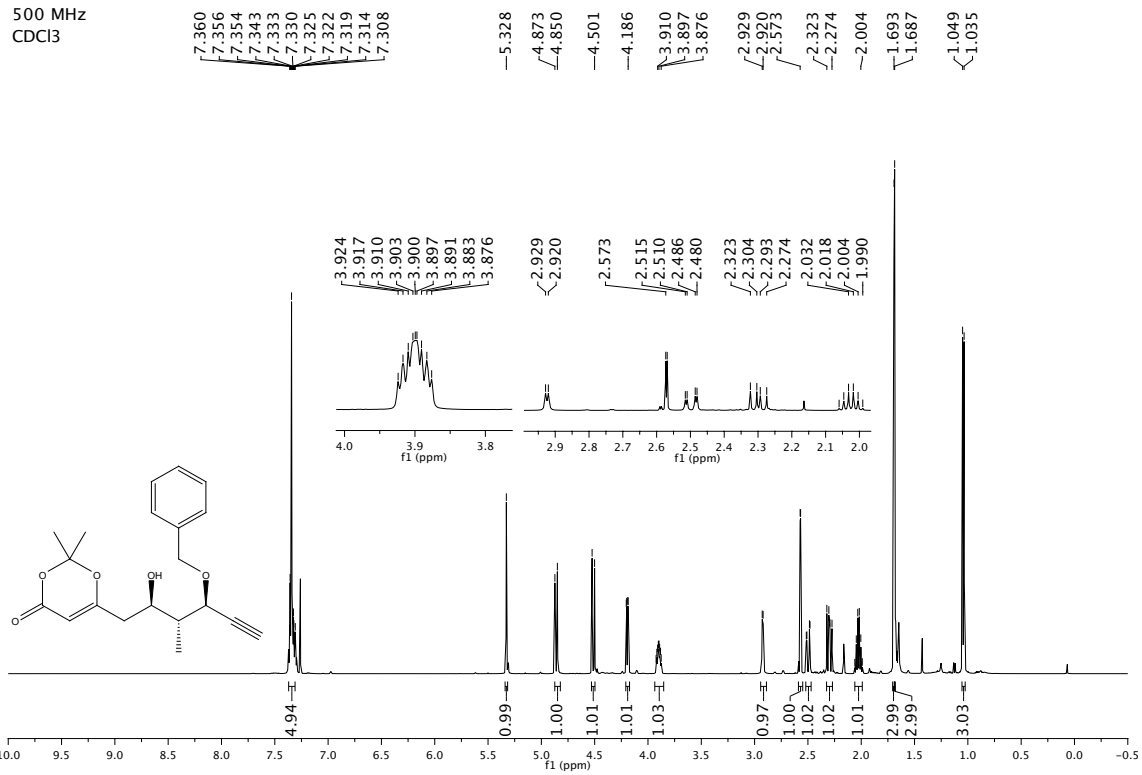


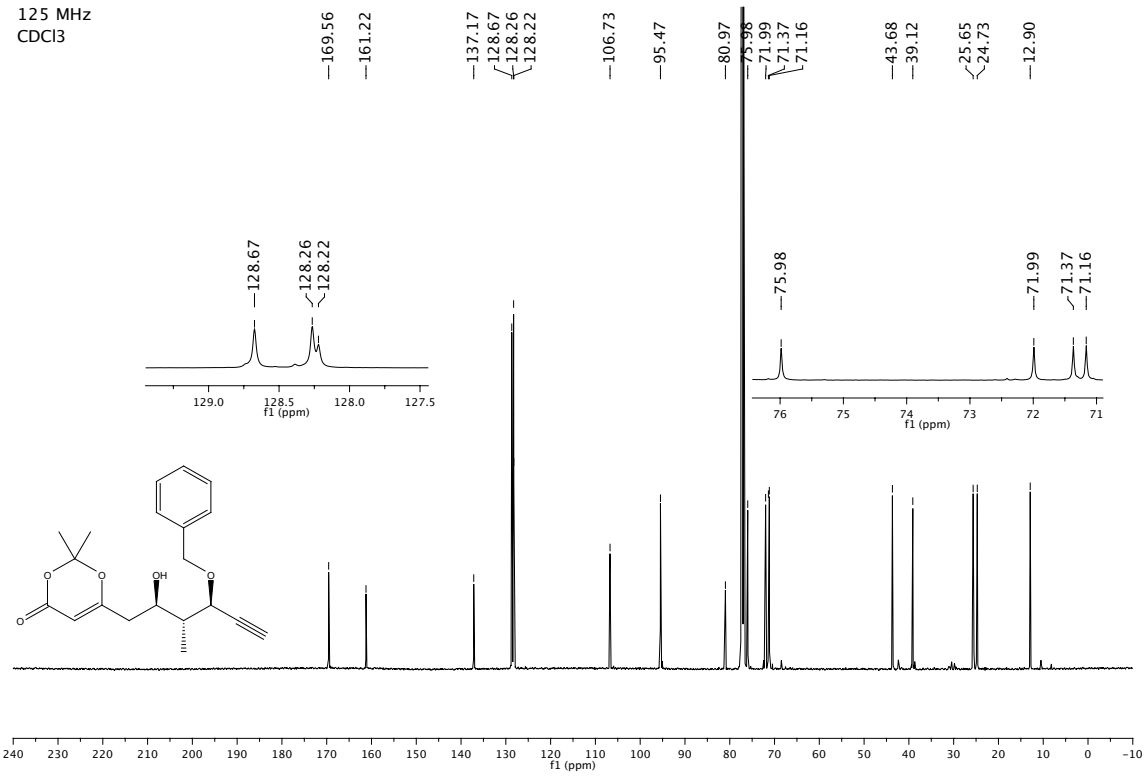
6-((2S,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **520**



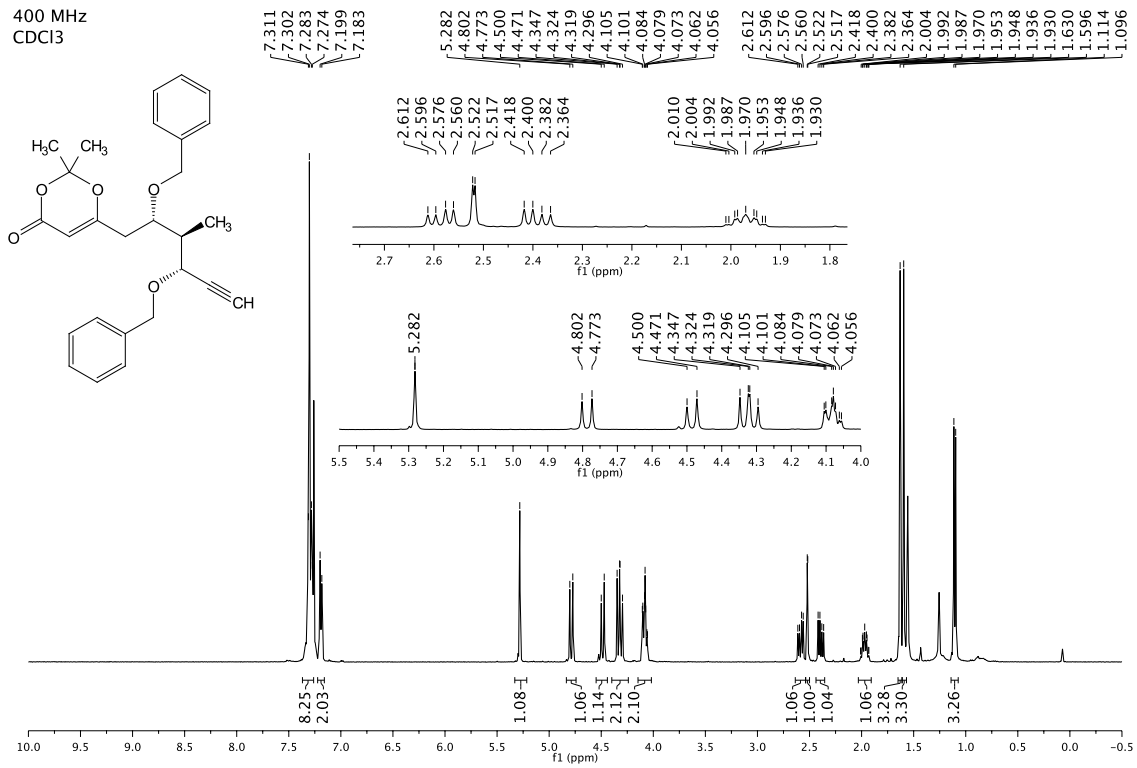


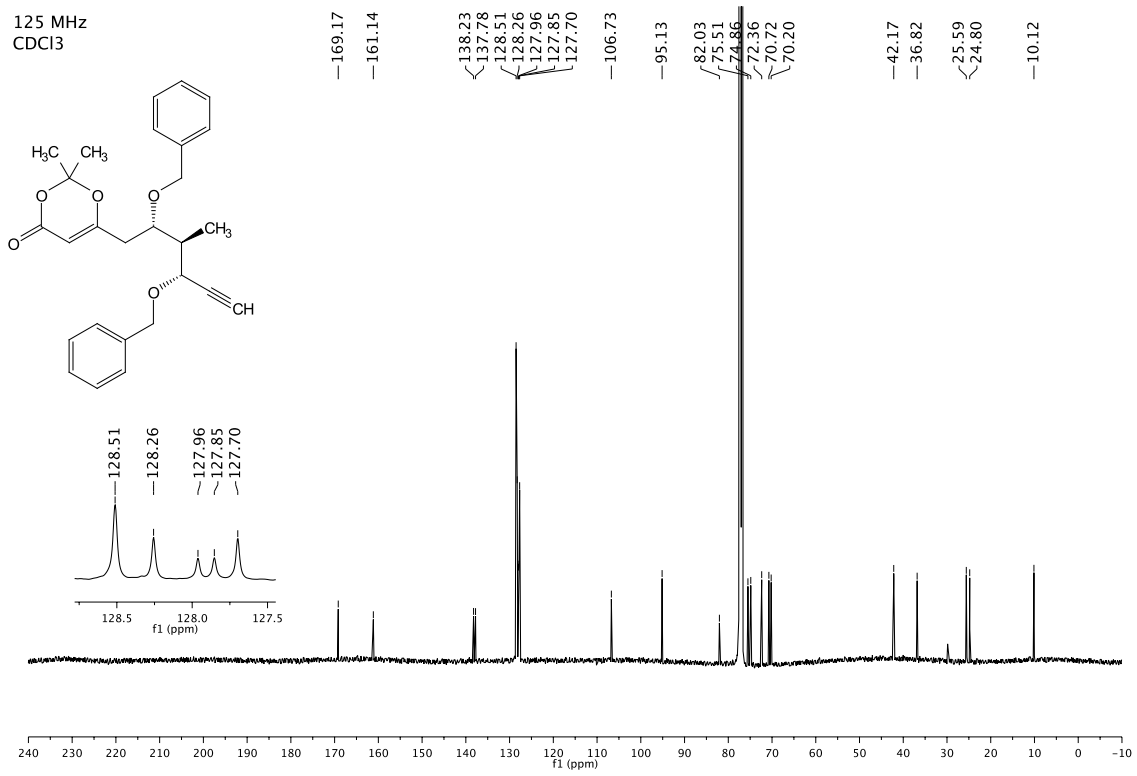
*6-((2R,3R,4R)-4-(benzyloxy)-2-hydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one epi-***520**



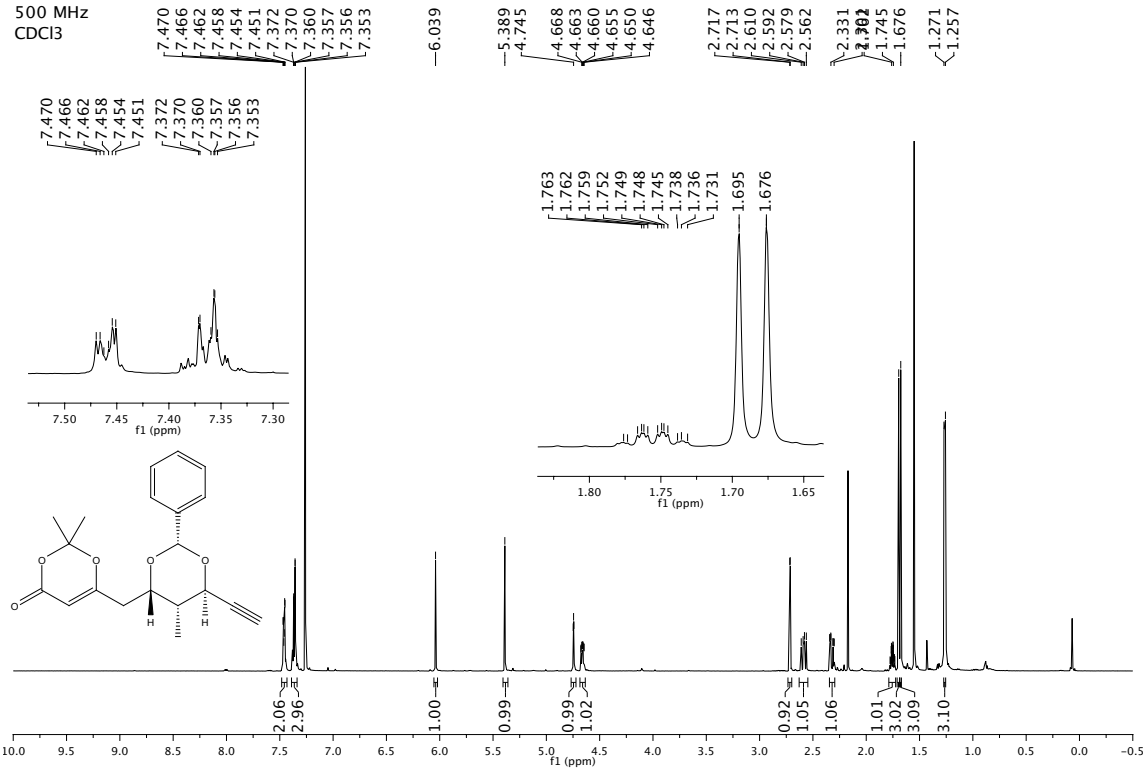


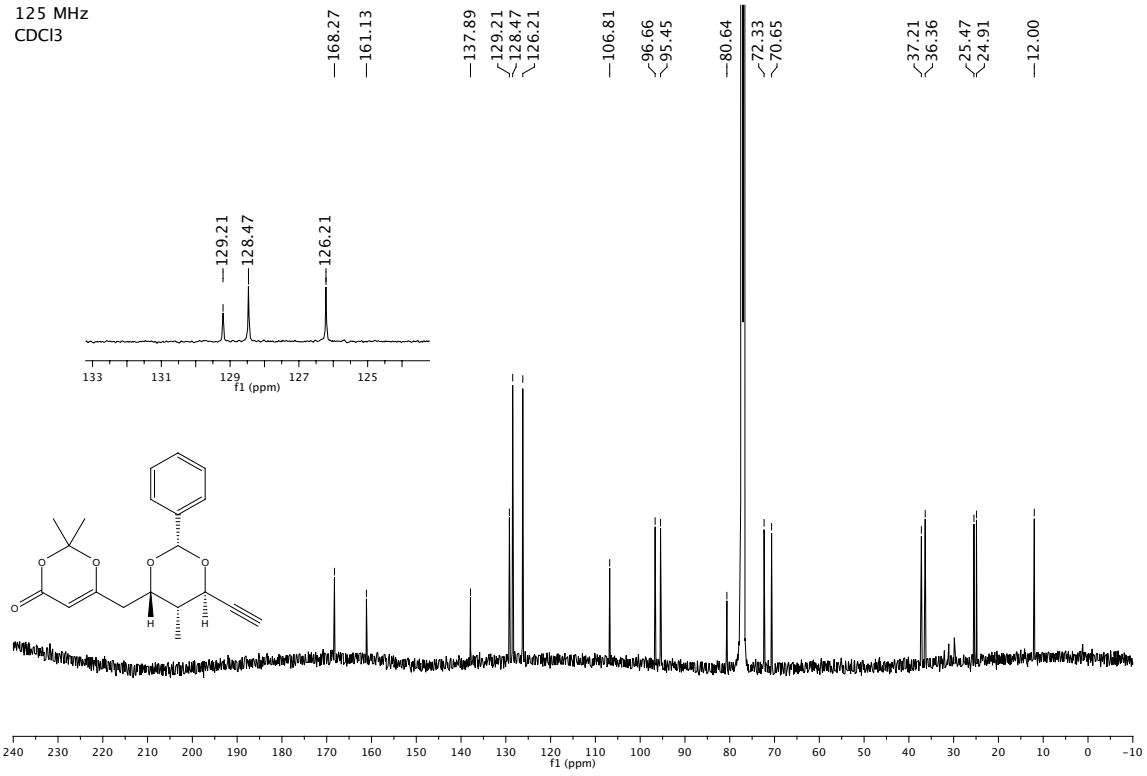
6-((2S,3R,4R)-2,4-bis(benzyloxy)-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **521**



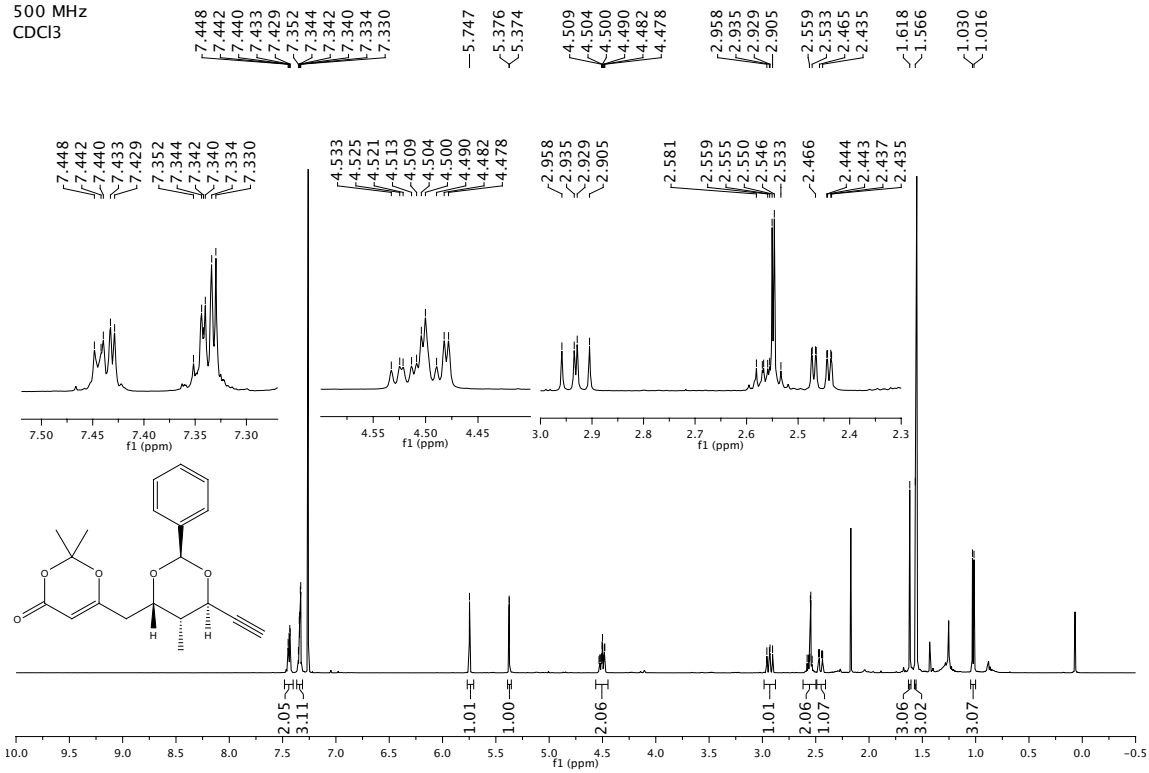


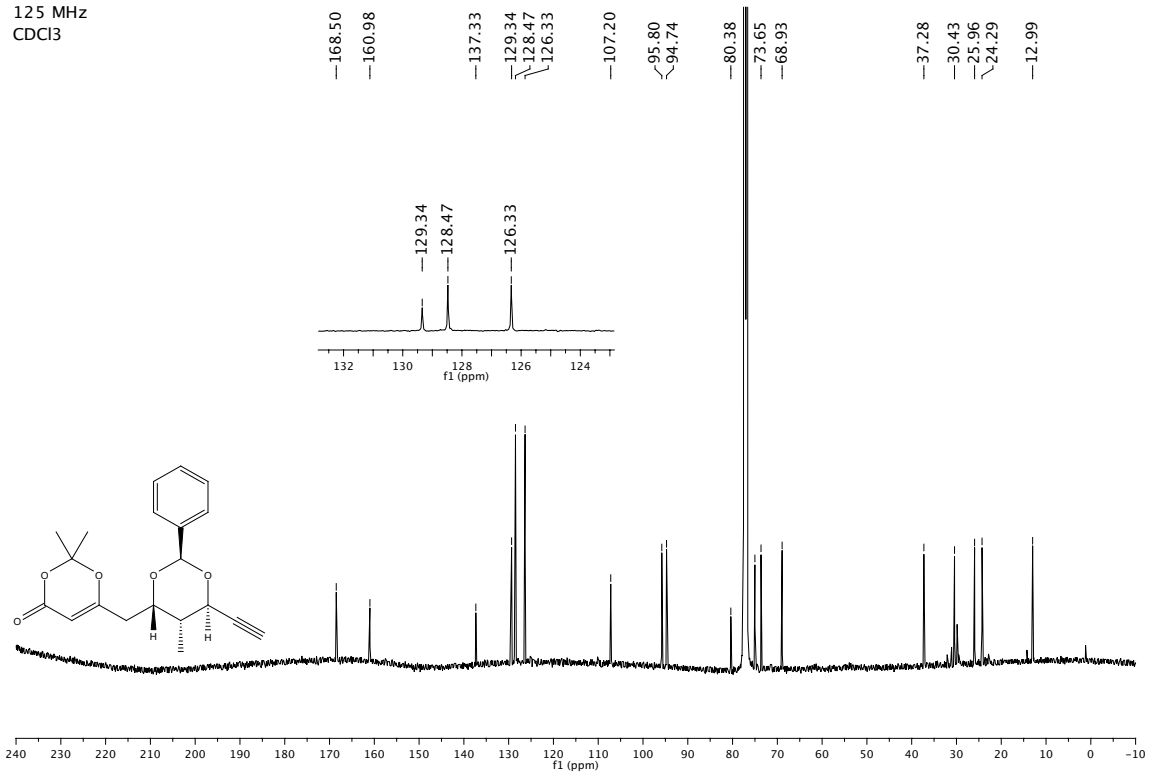
6-(((2S,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **525**



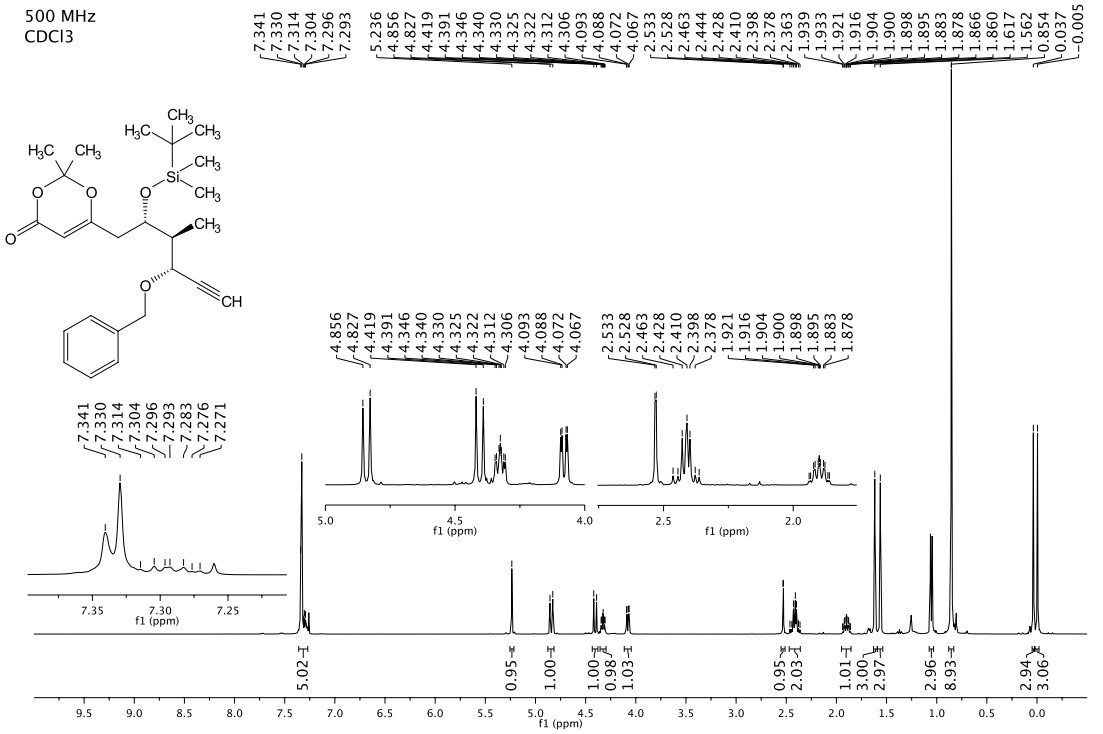


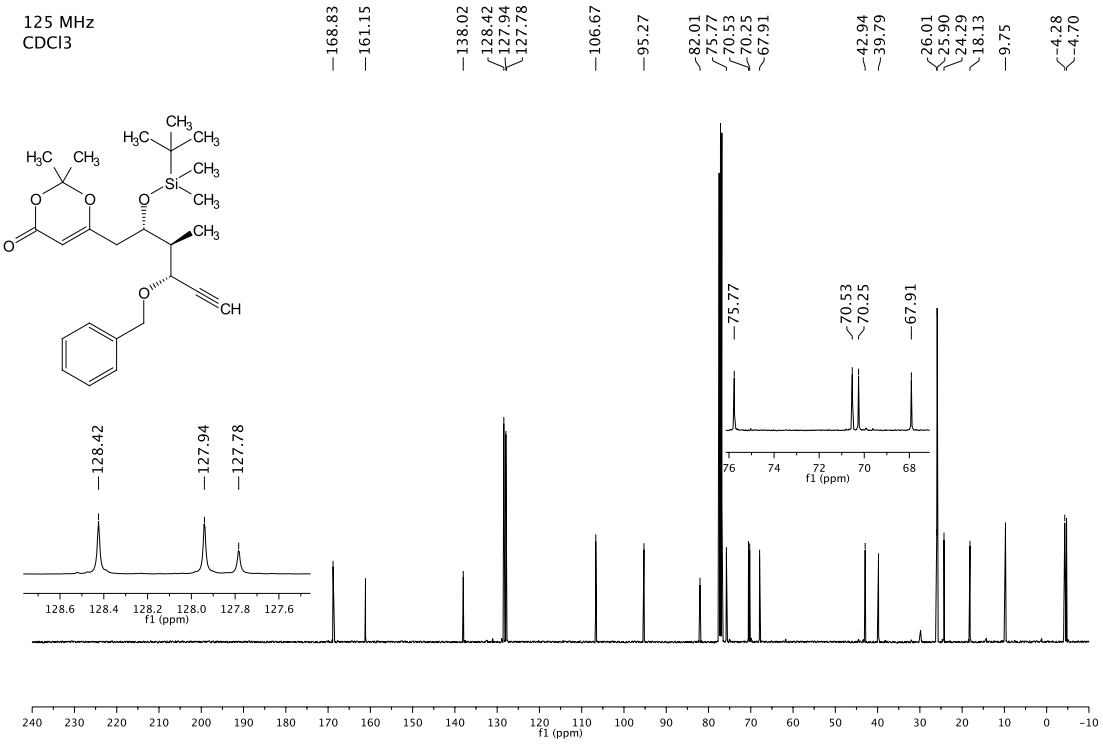
6-(((2R,4S,5R,6R)-6-ethynyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **524**



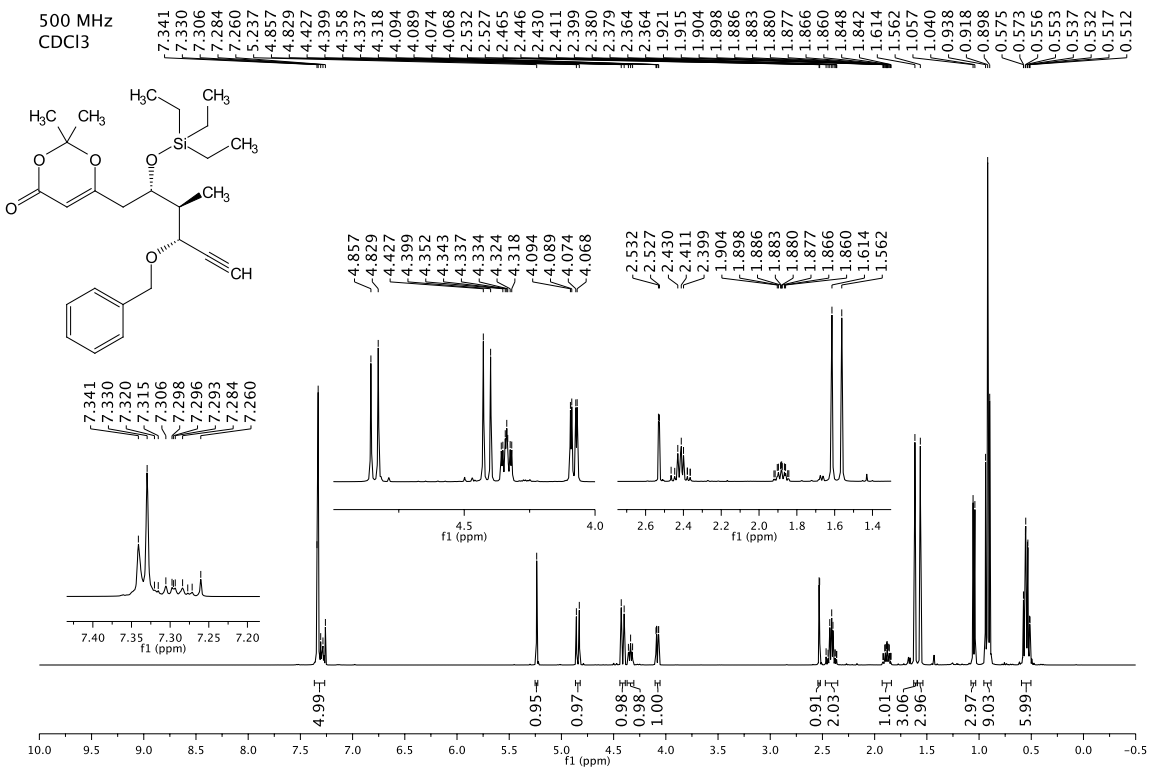


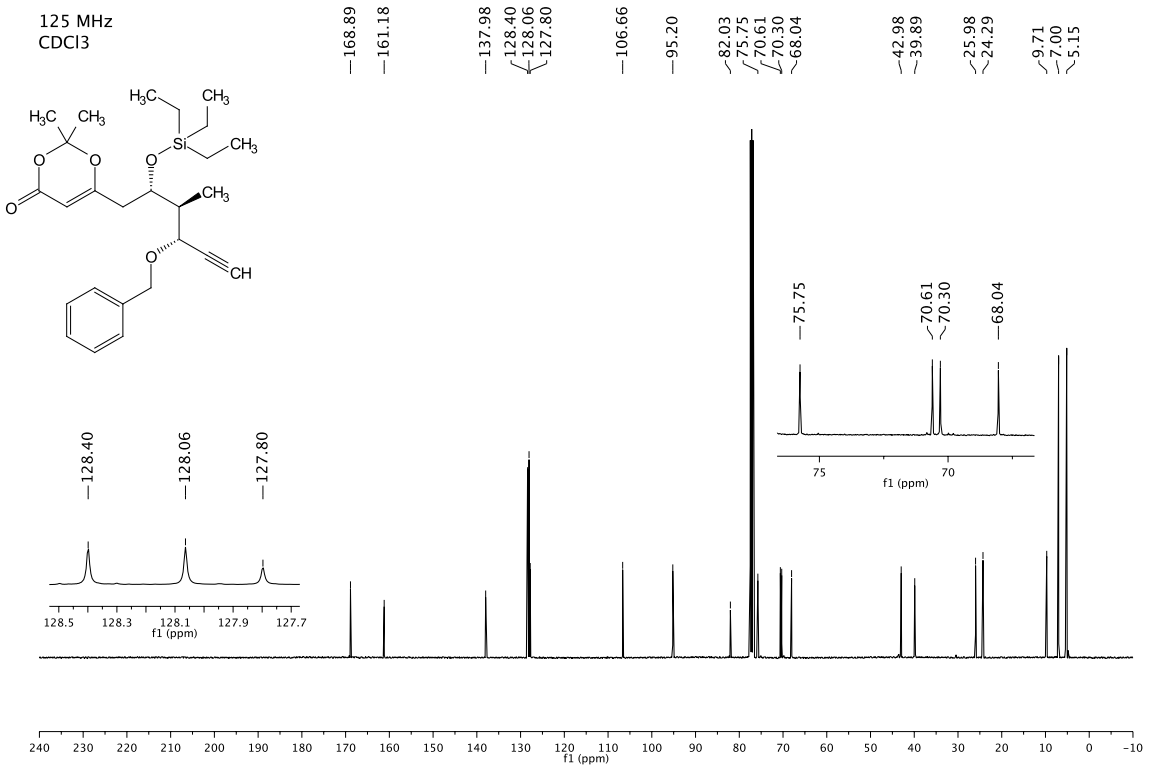
6-((2S,3S,4R)-4-(benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **526**





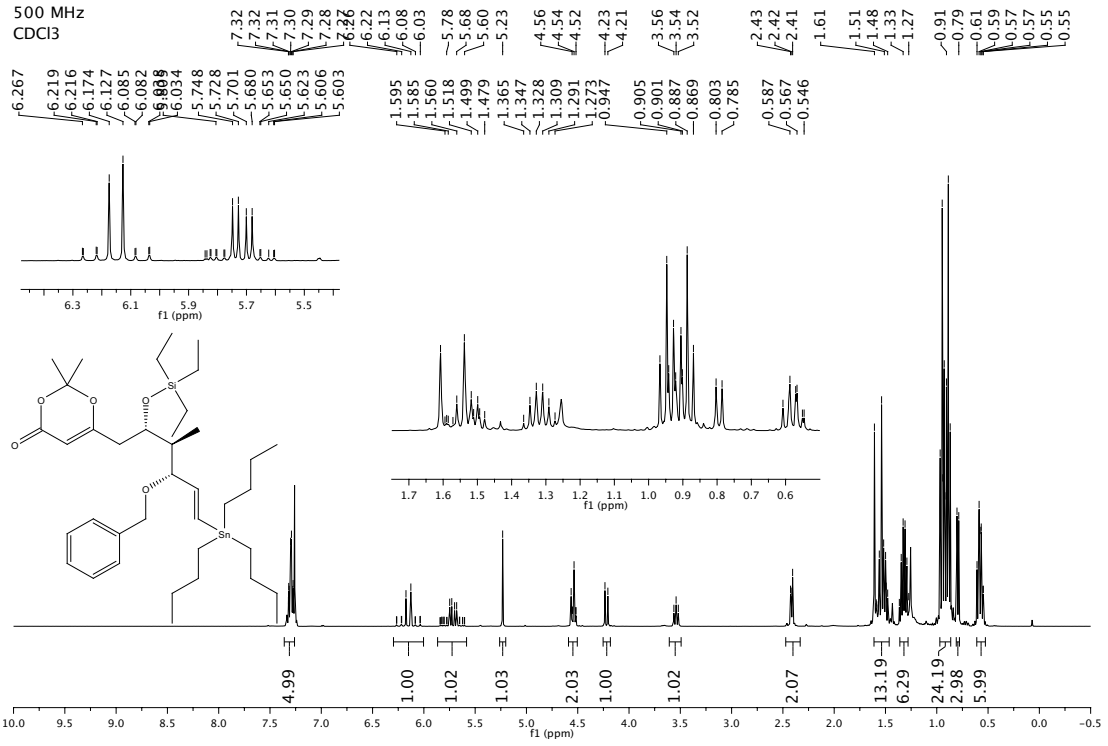
6-((2S,3S,4R)-4-(benzyloxy)-3-methyl-2-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **527**

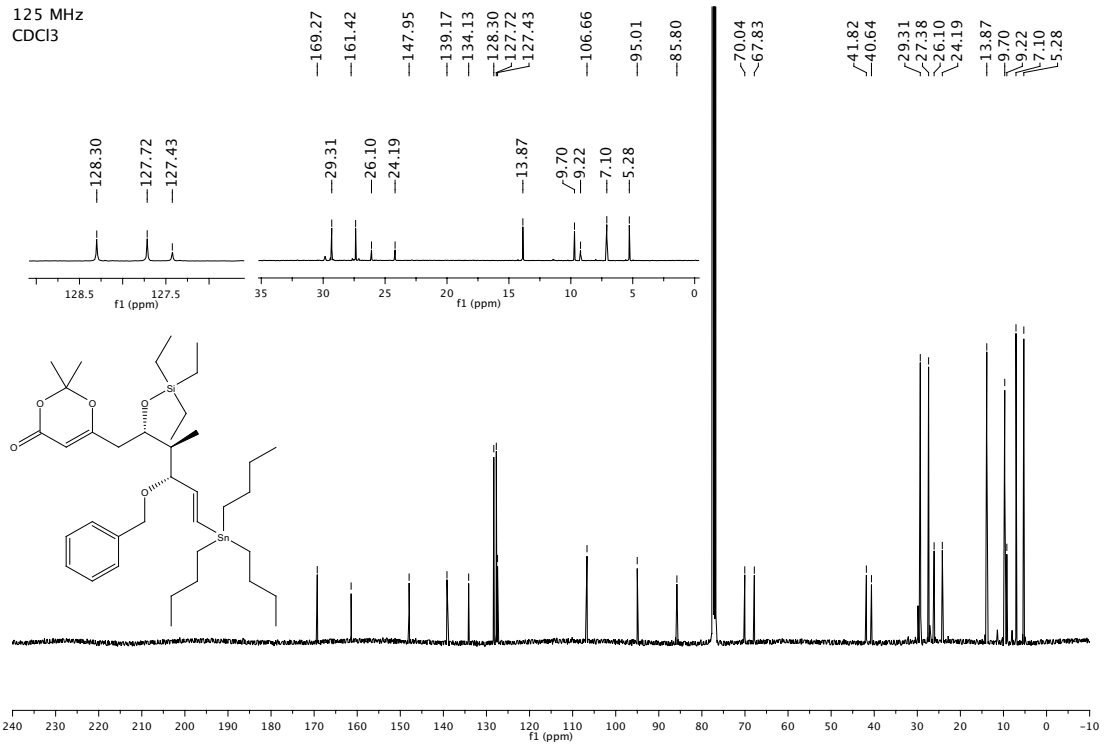




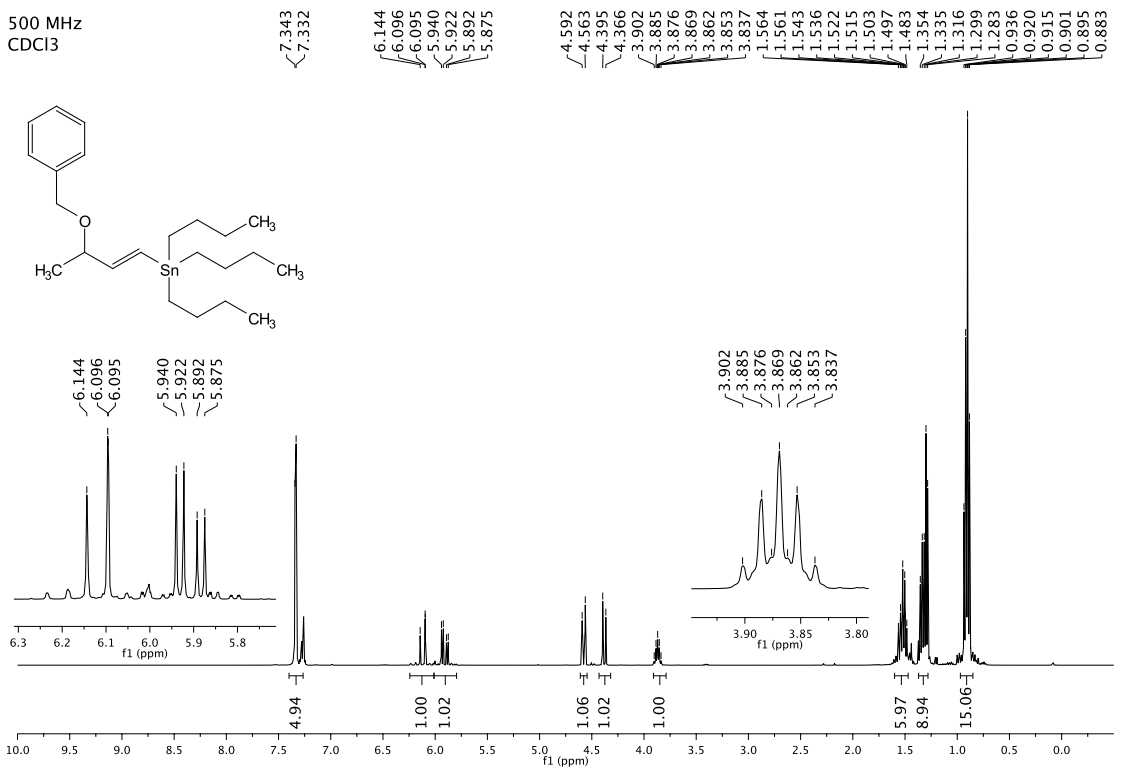
viii.2.3 Second generation

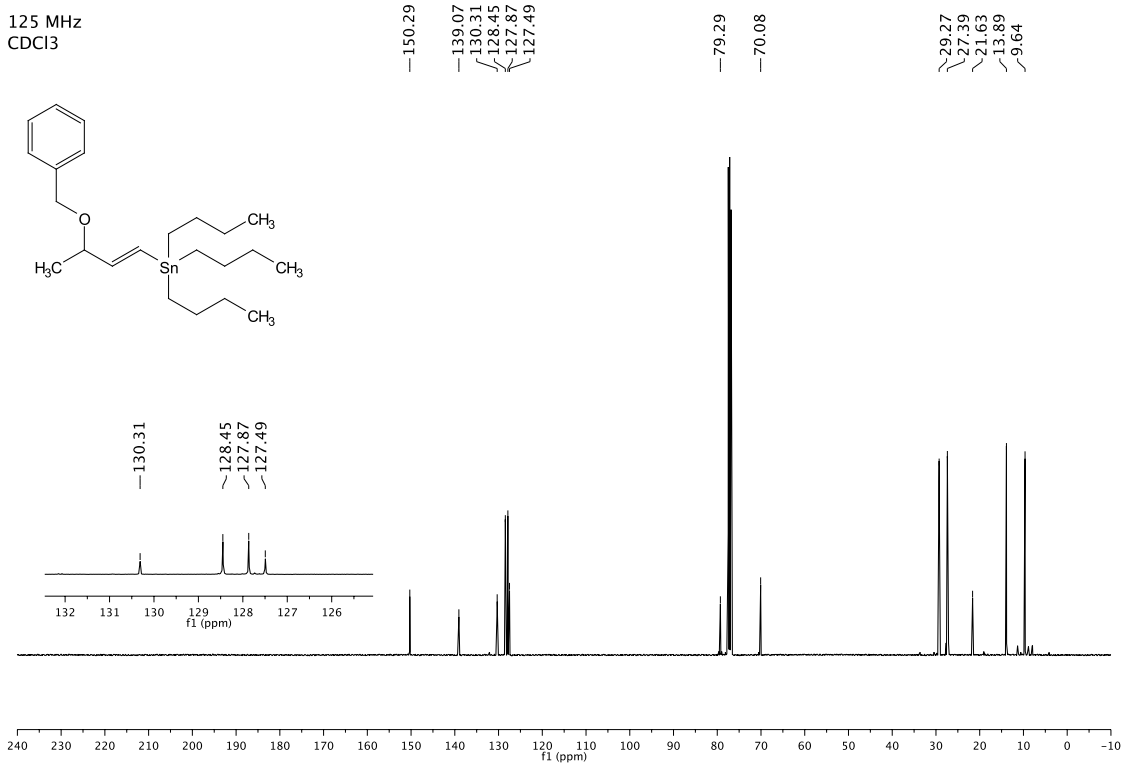
6-((2S,3S,4R,E)-4-(benzyloxy)-3-methyl-6-(tributylstannyl)-2-((triethylsilyl)oxy)hex-5-en-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **534**



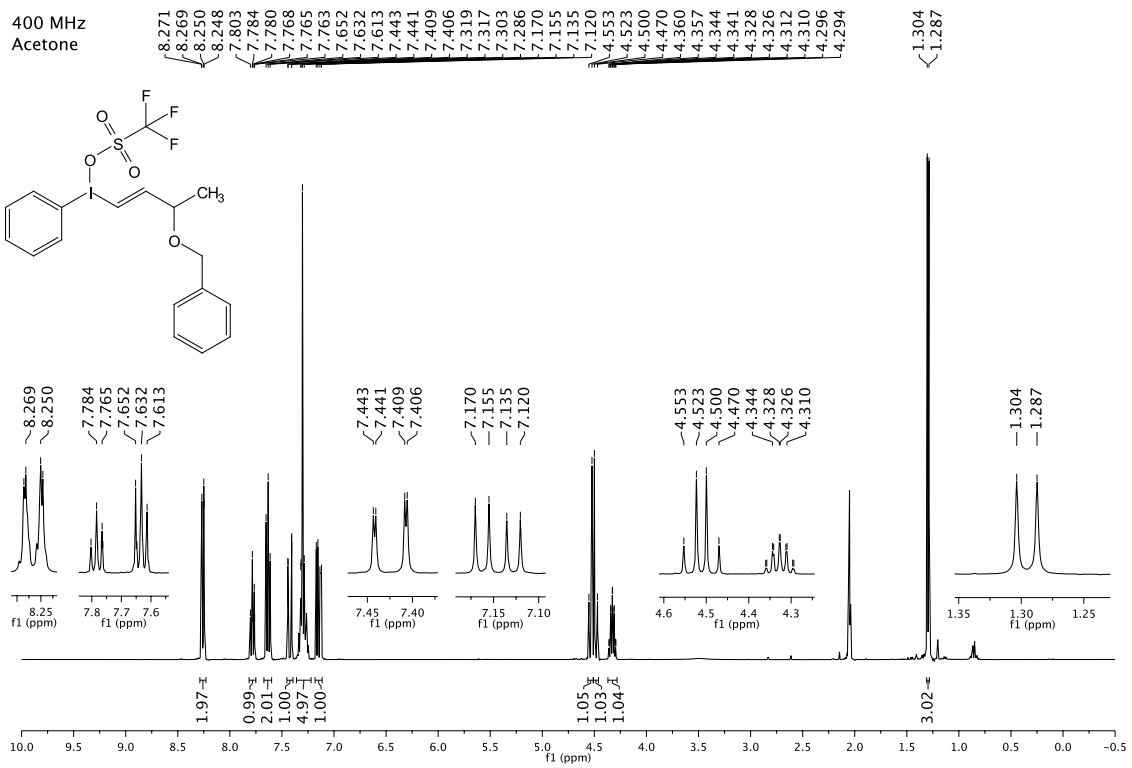


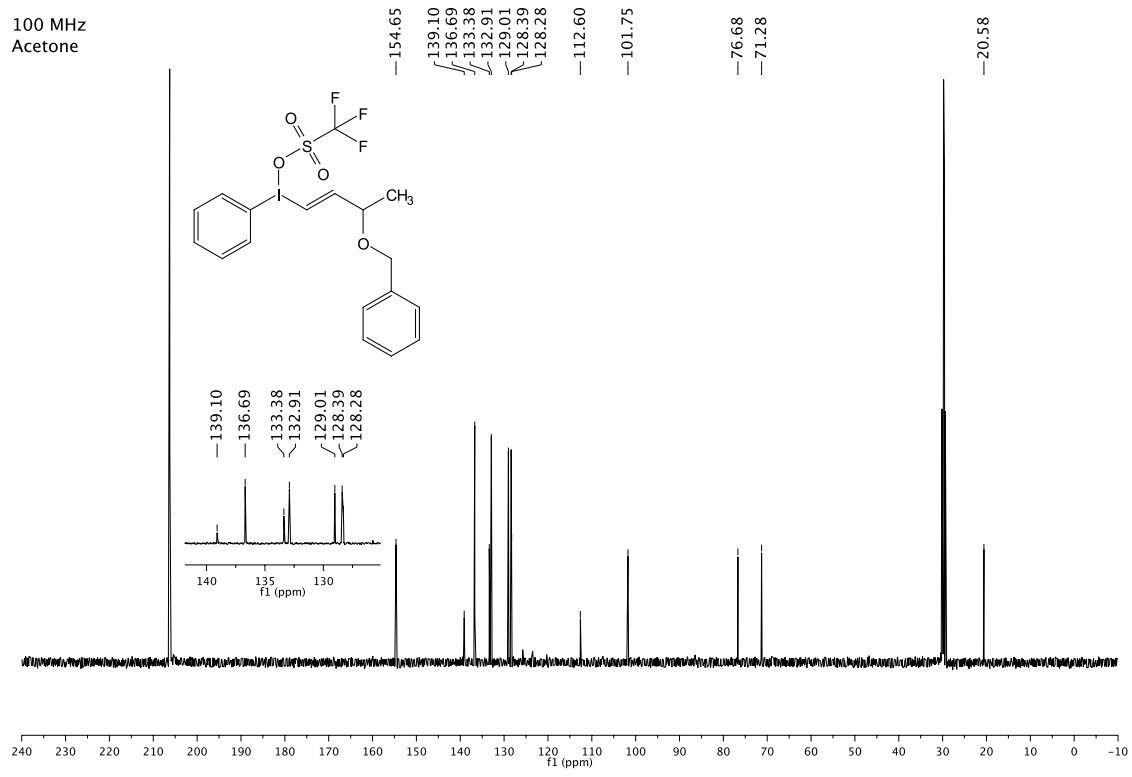
(E)-(3-(benzyloxy)but-1-en-1-yl)tributylstannane **540**



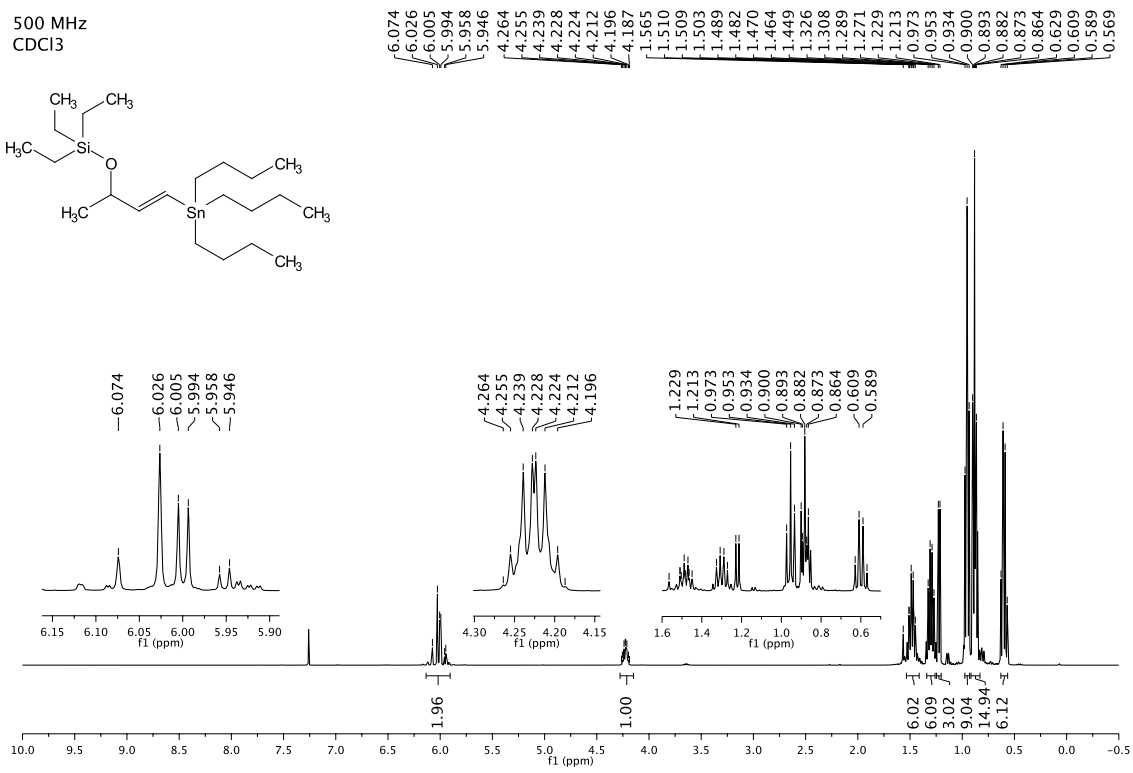


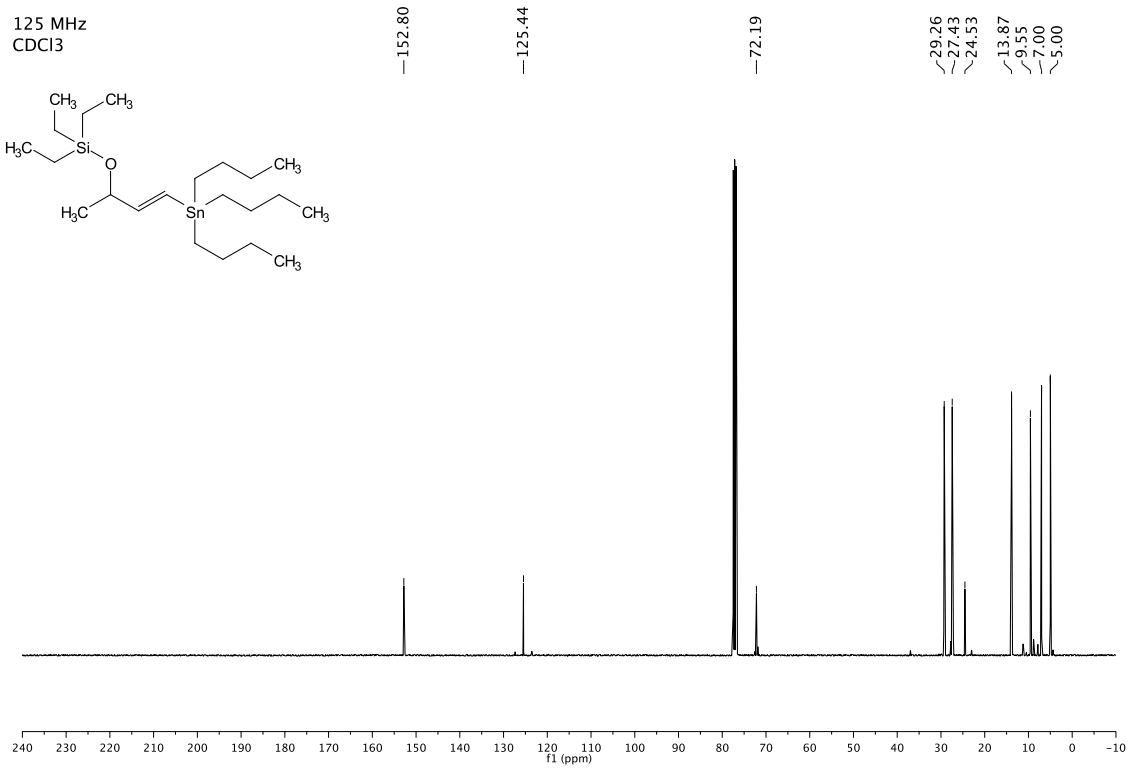
(E)-(3-(benzyloxy)but-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate **541**



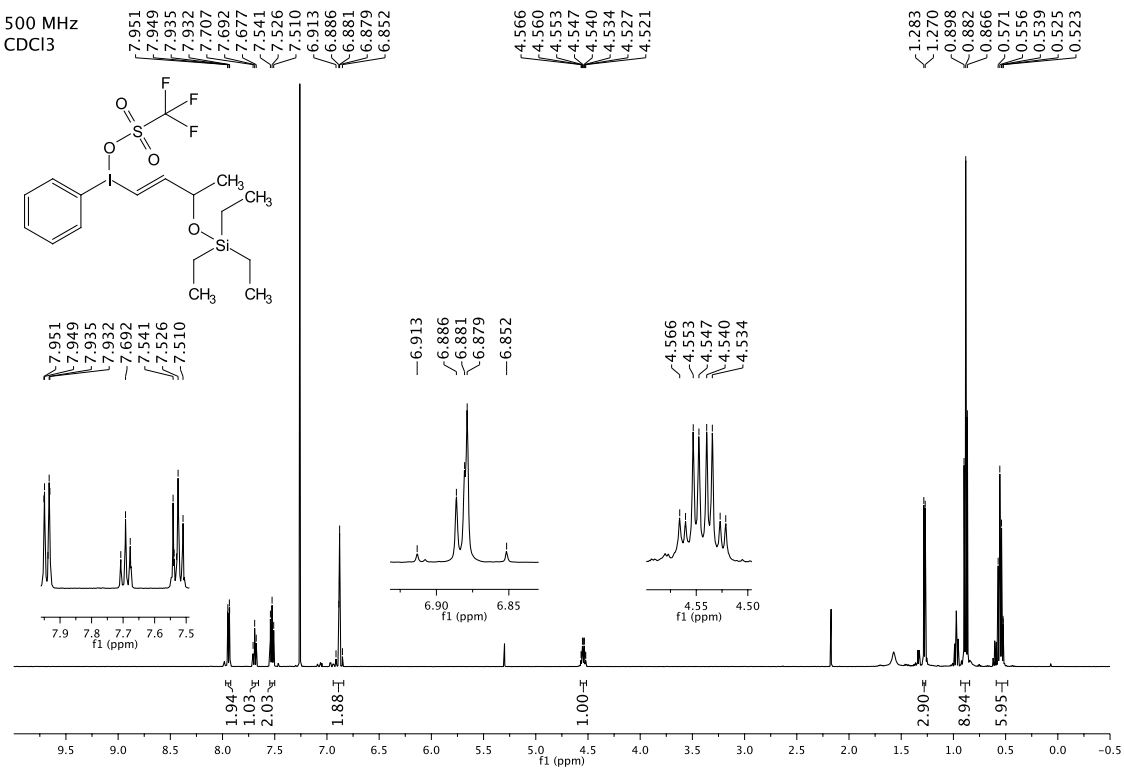


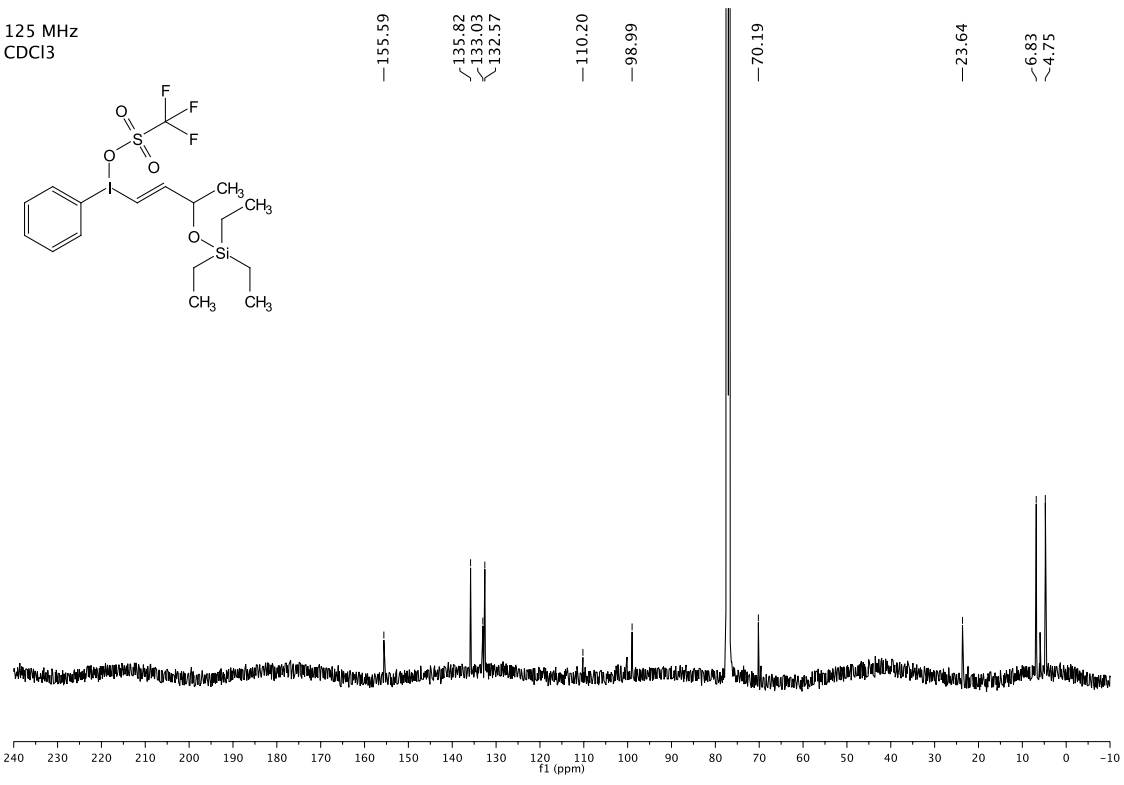
(E)-triethyl((4-(tributylstannyl)but-3-en-2-yl)oxy)silane **542**



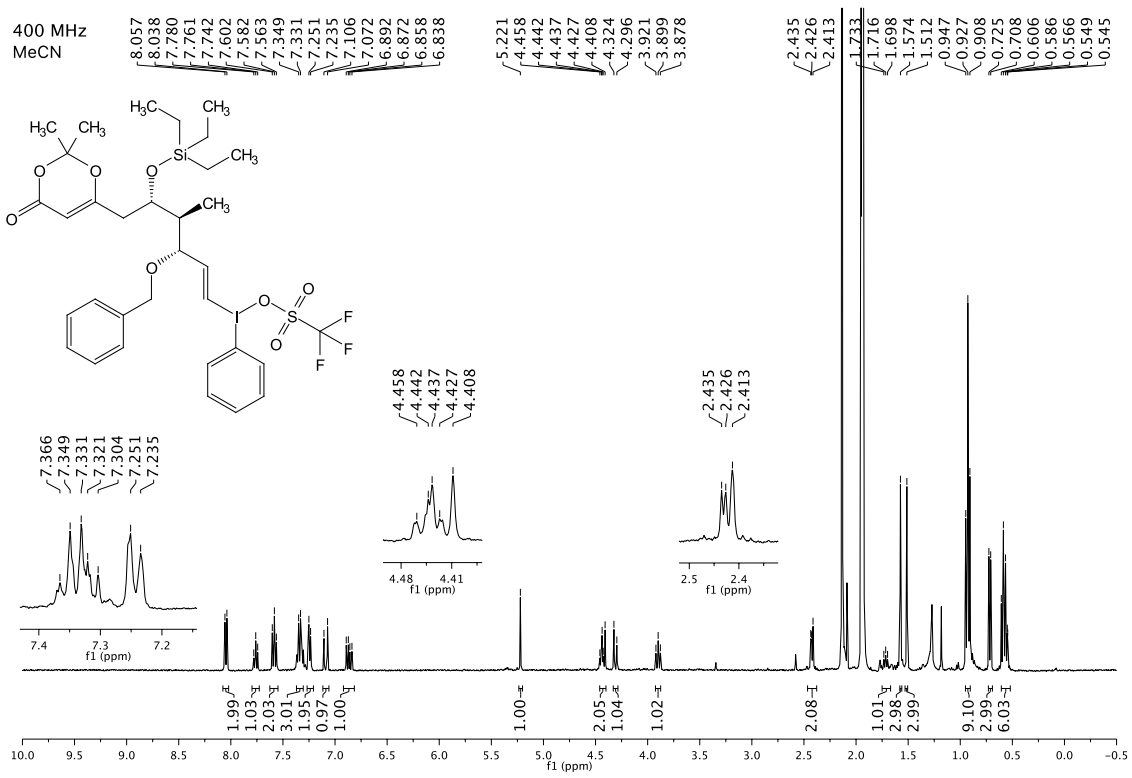


(E)-(3-((triethylsilyl)oxy)but-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate **543**

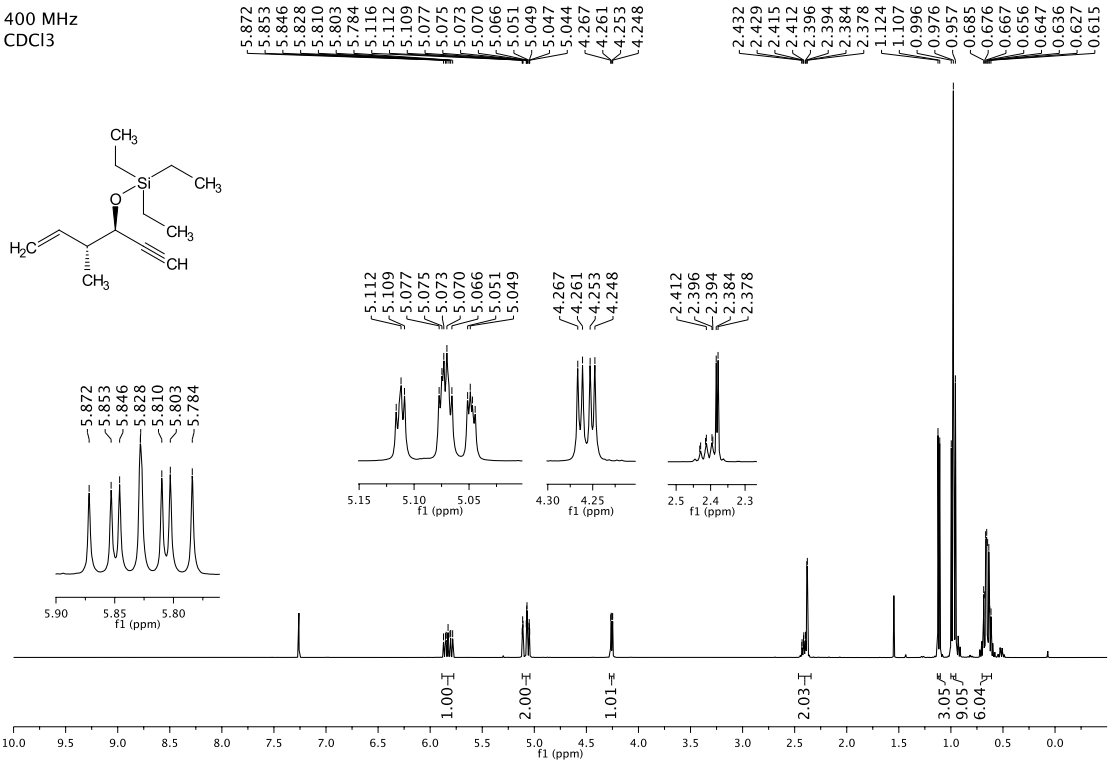


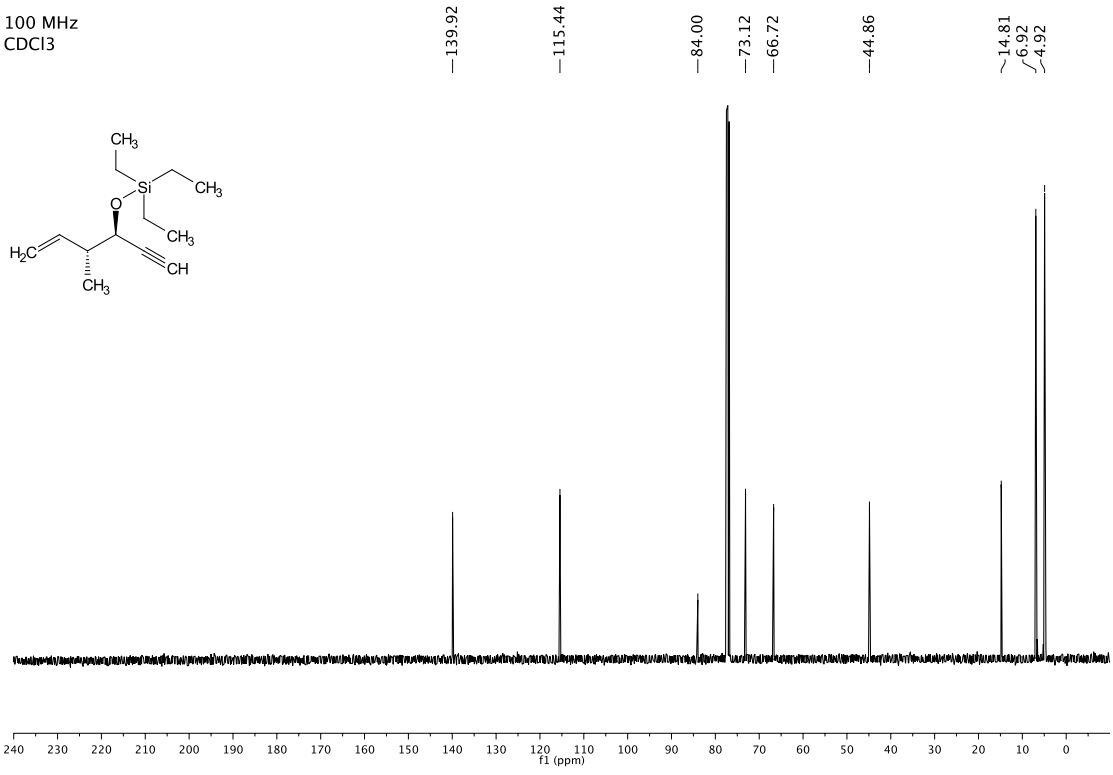


((3R,4S,5S,E)-3-(benzyloxy)-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-4-methyl-5-((triethylsilyl)oxy)hex-1-en-1-yl)(phenyl)-iodonium trifluoromethanesulfonate **536**

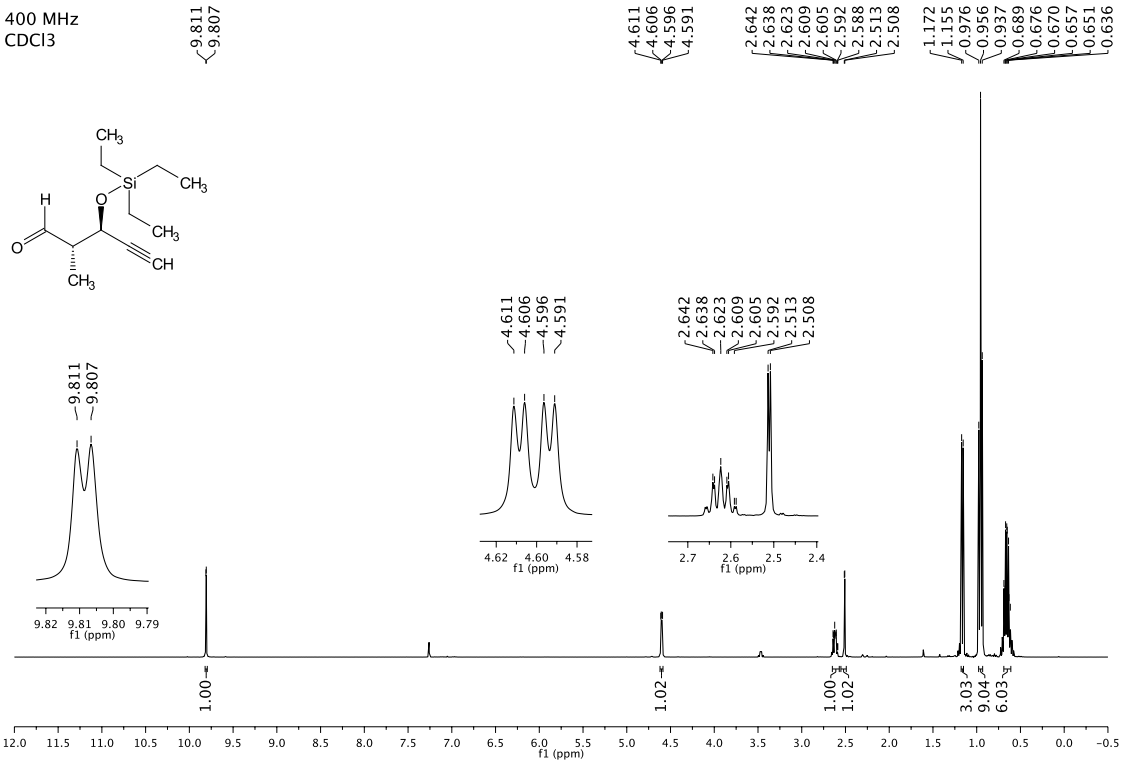


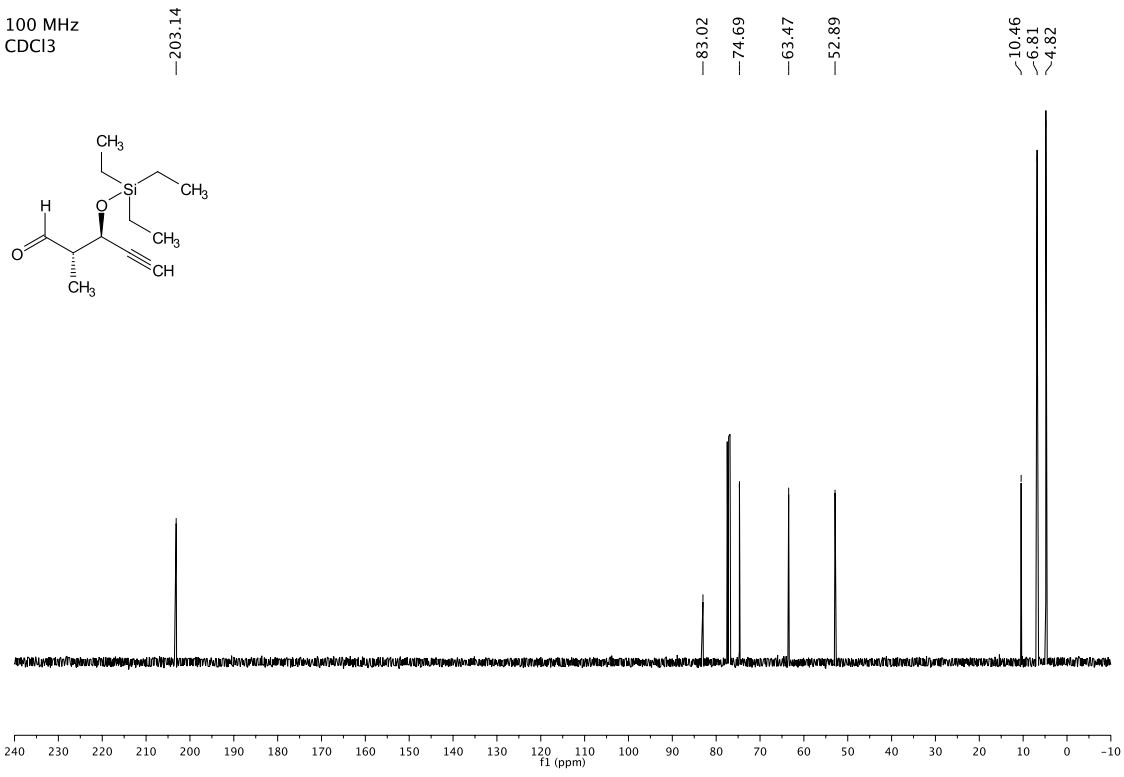
triethyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane **550**



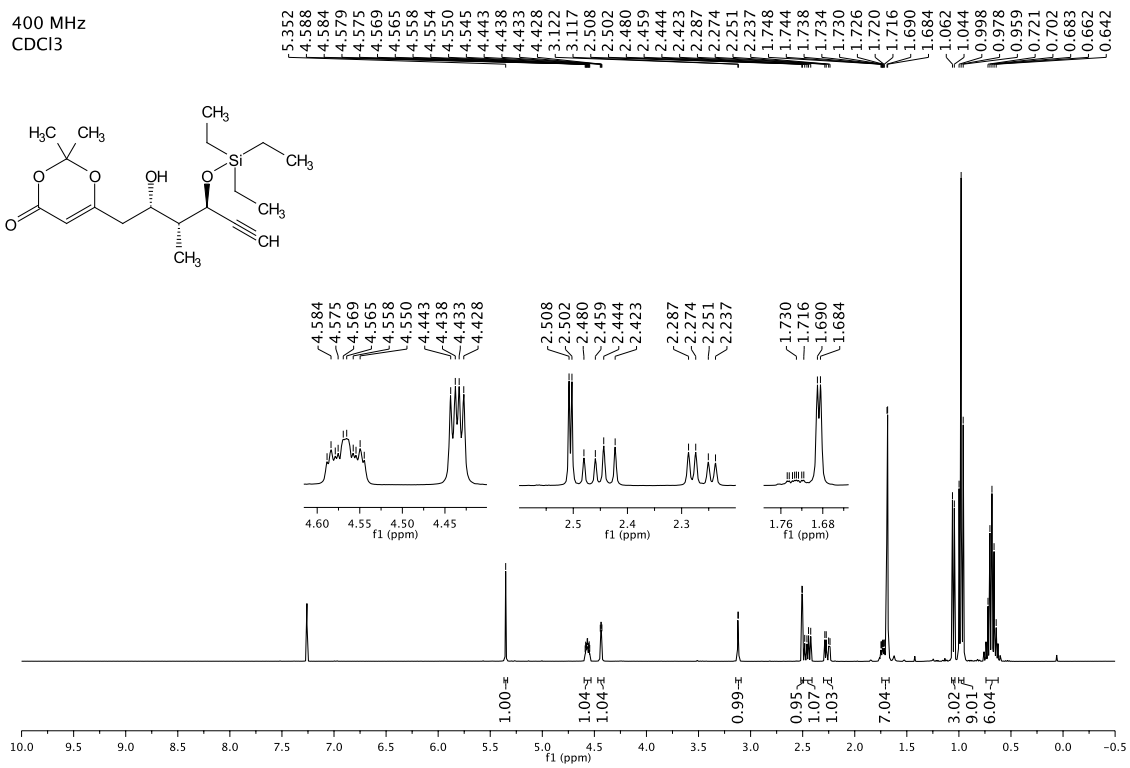


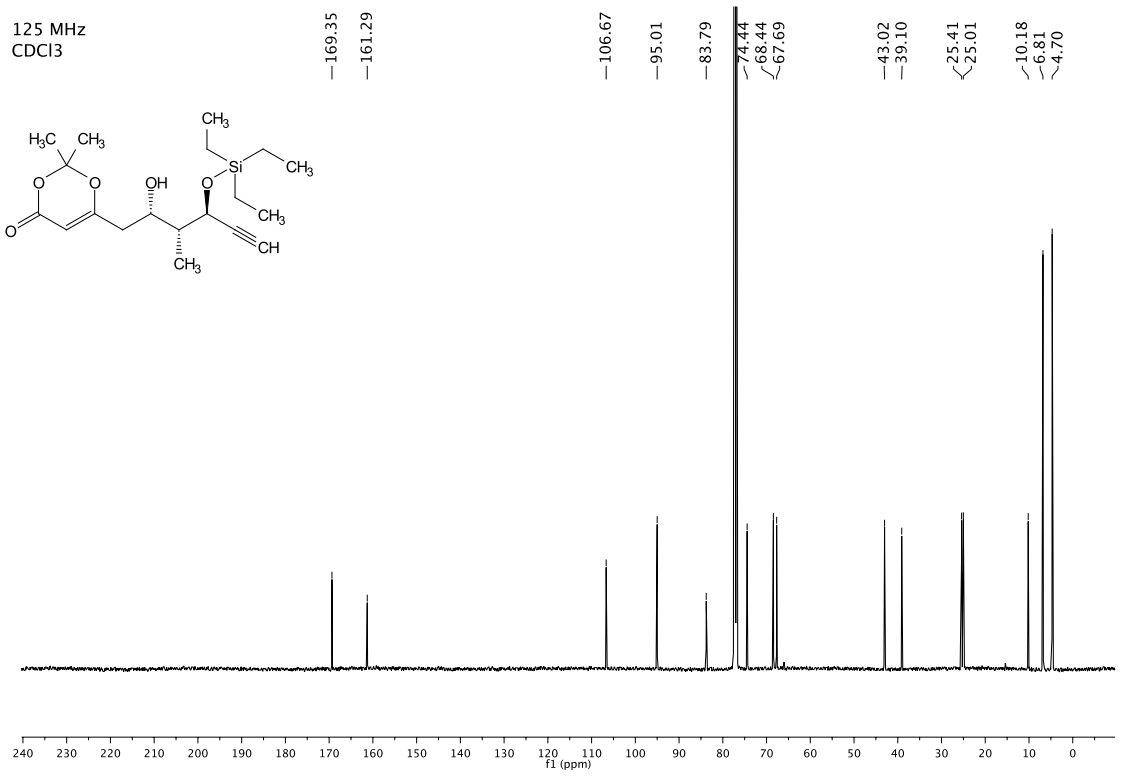
(2S,3R)-2-methyl-3-((triethylsilyl)oxy)pent-4-ynal **549**



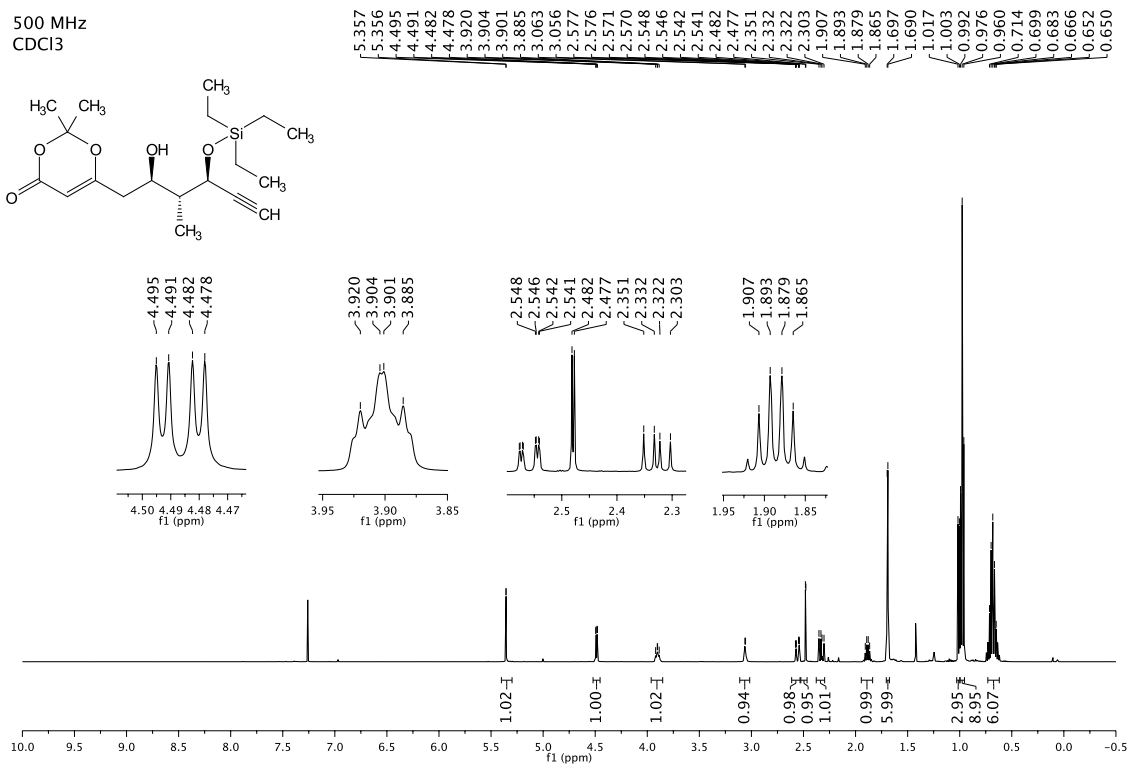


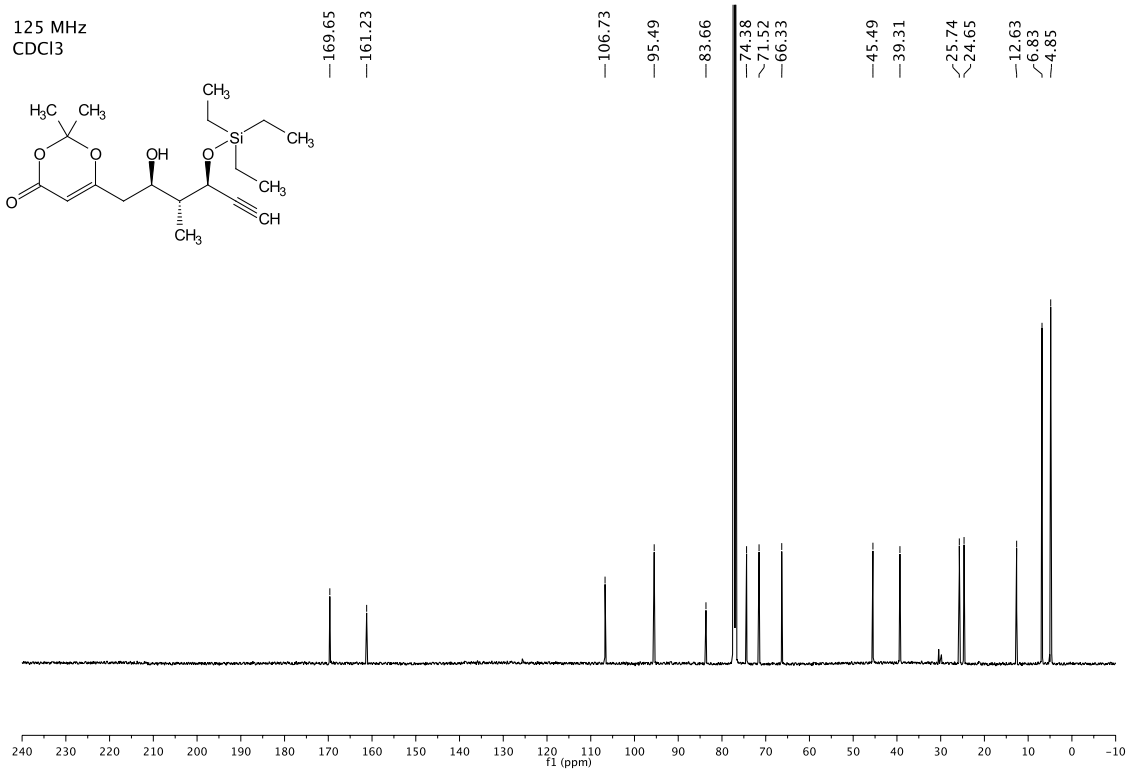
6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **548**



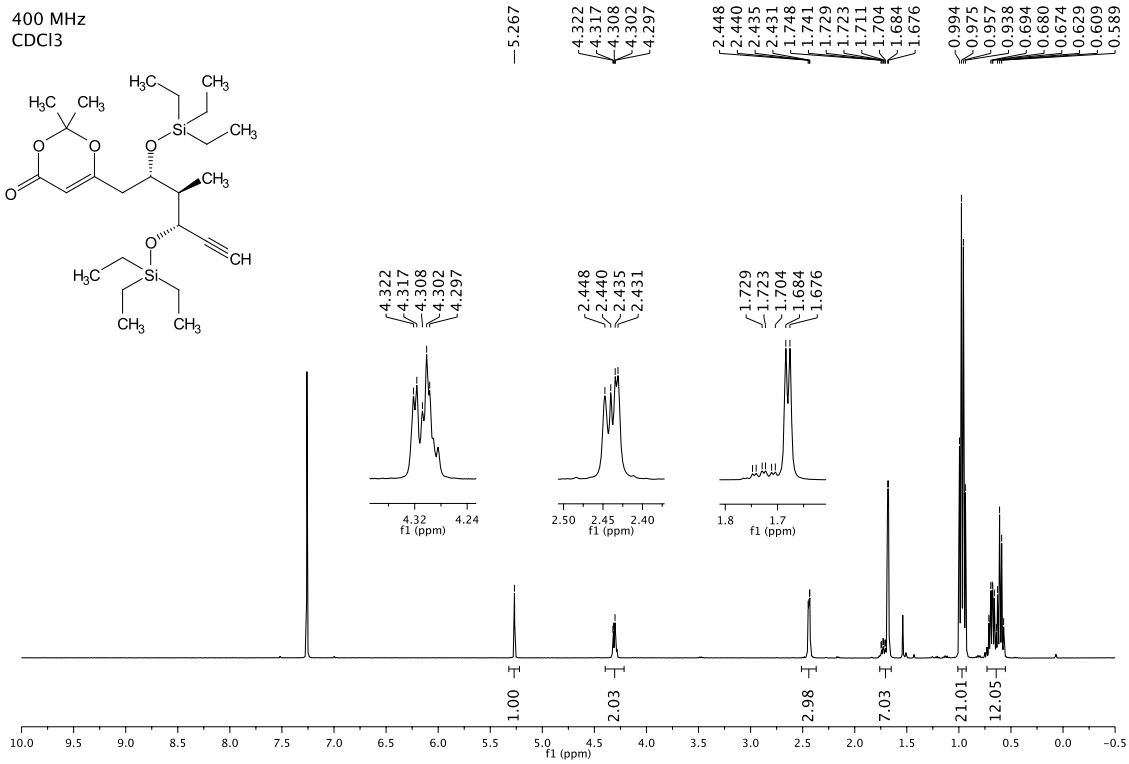


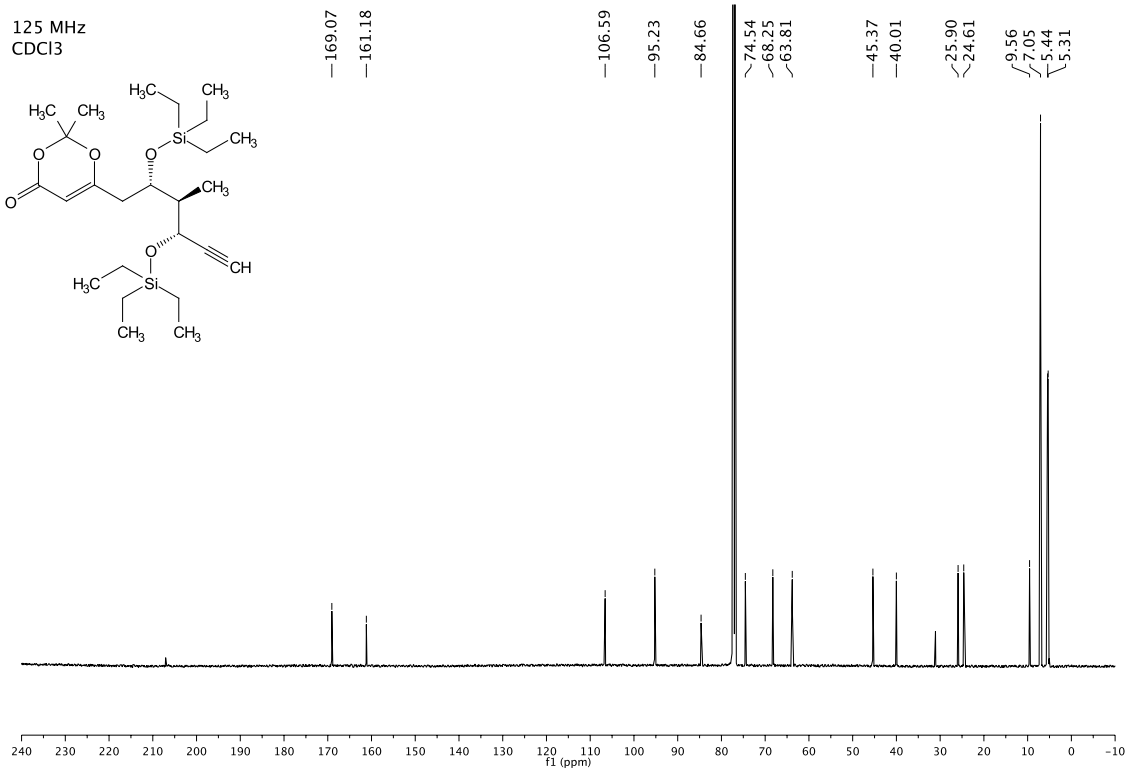
*6-((2R,3R,4R)-2-hydroxy-3-methyl-4-((triethylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one epi-***548**



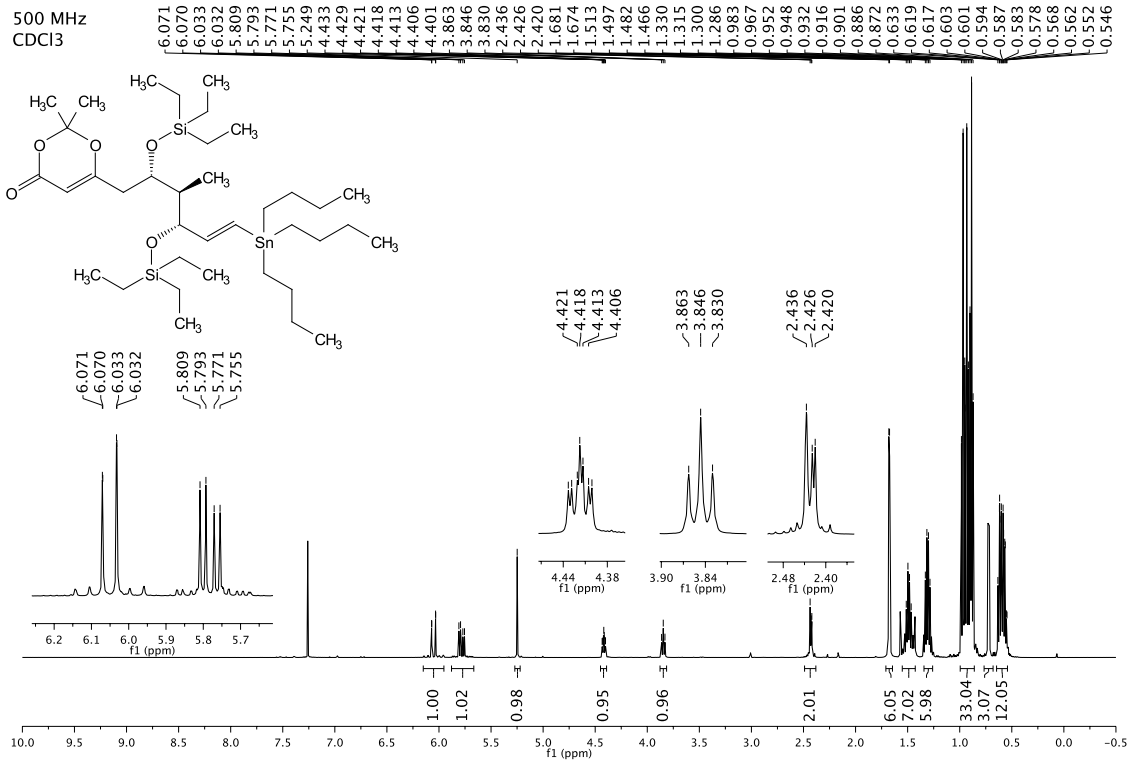


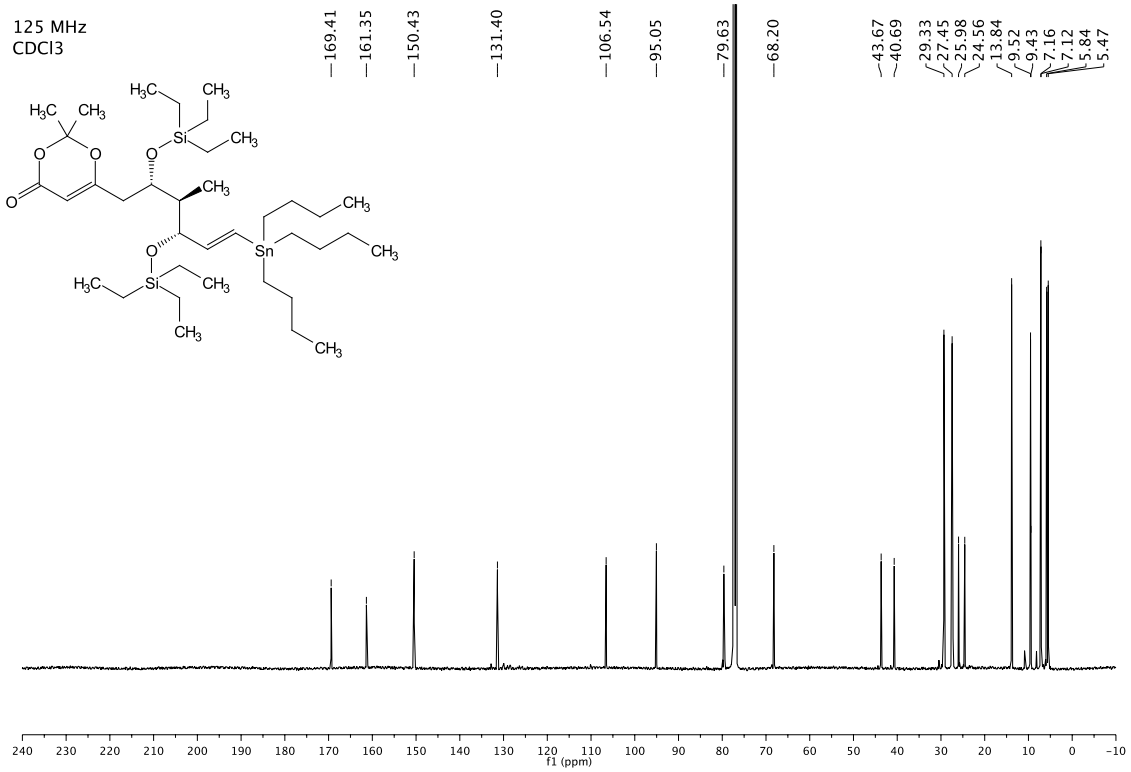
2,2-dimethyl-6-((2S,3R,4R)-3-methyl-2,4-bis((triethylsilyl)oxy)hex-5-yn-1-yl)-4H-1,3-dioxin-4-one **547**



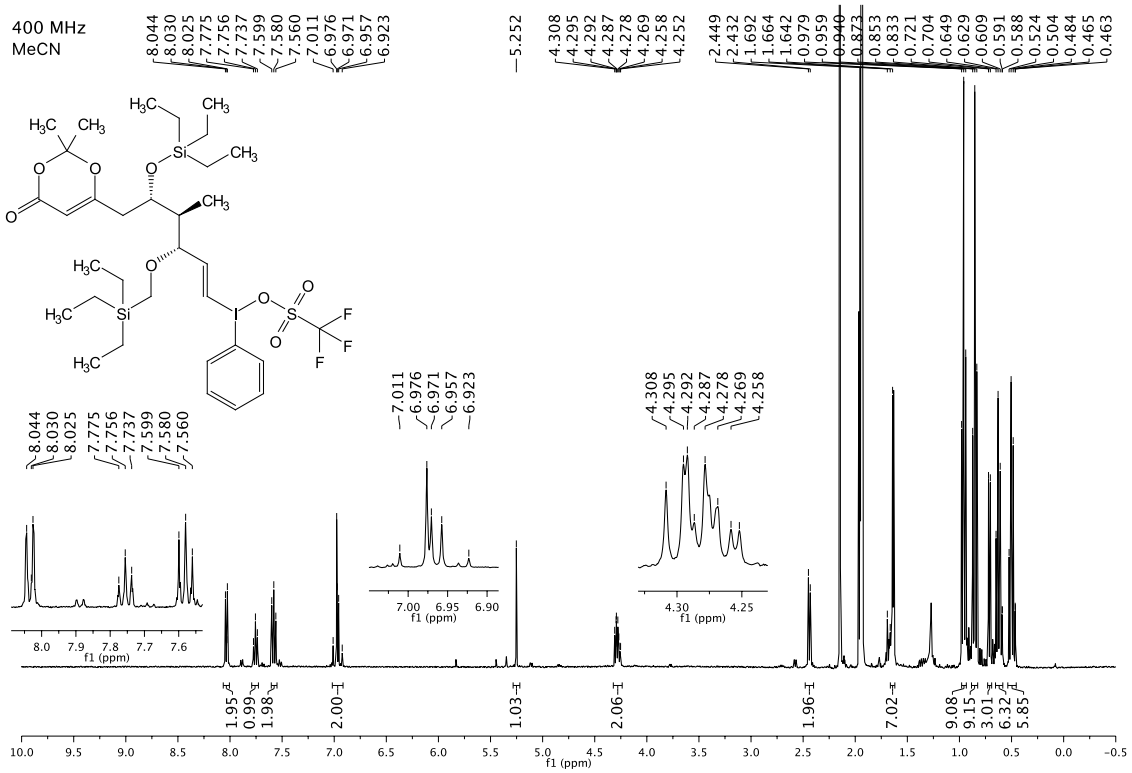


2,2-dimethyl-6-((2S,3R,4R,E)-3-methyl-6-(tributylstannyl)-2,4-bis((triethylsilyl)oxy)hex-5-en-1-yl)-4H-1,3-dioxin-4-one **546**

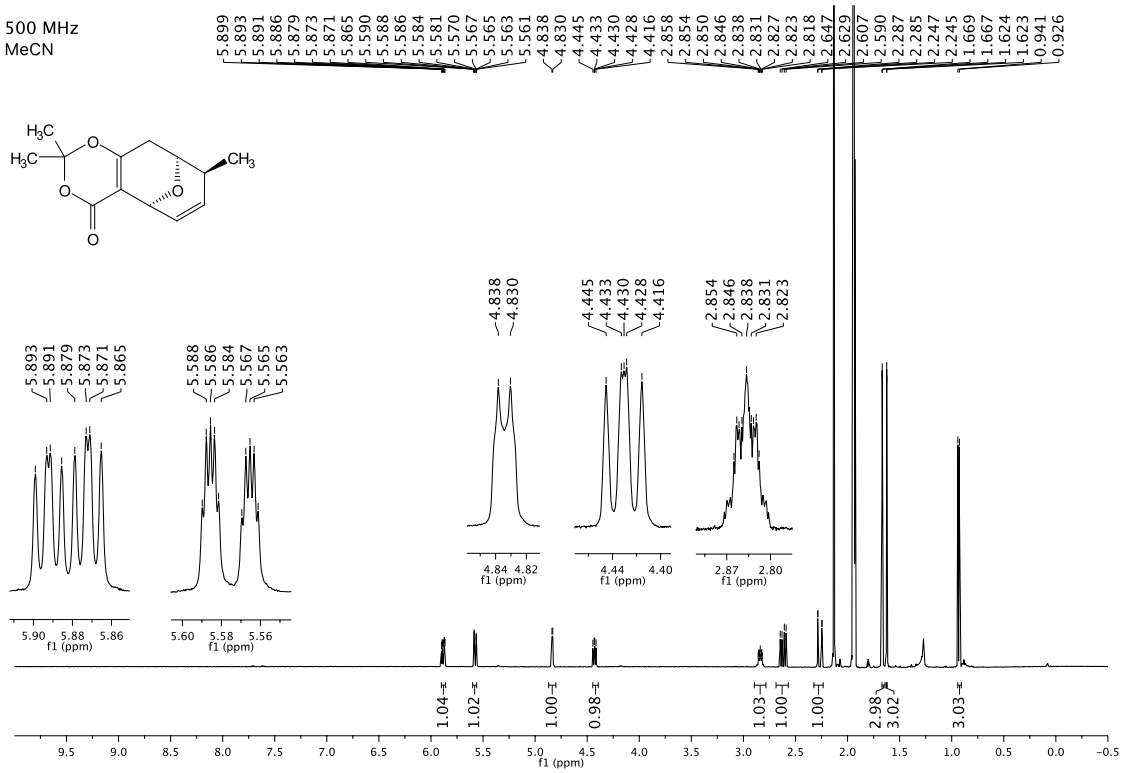


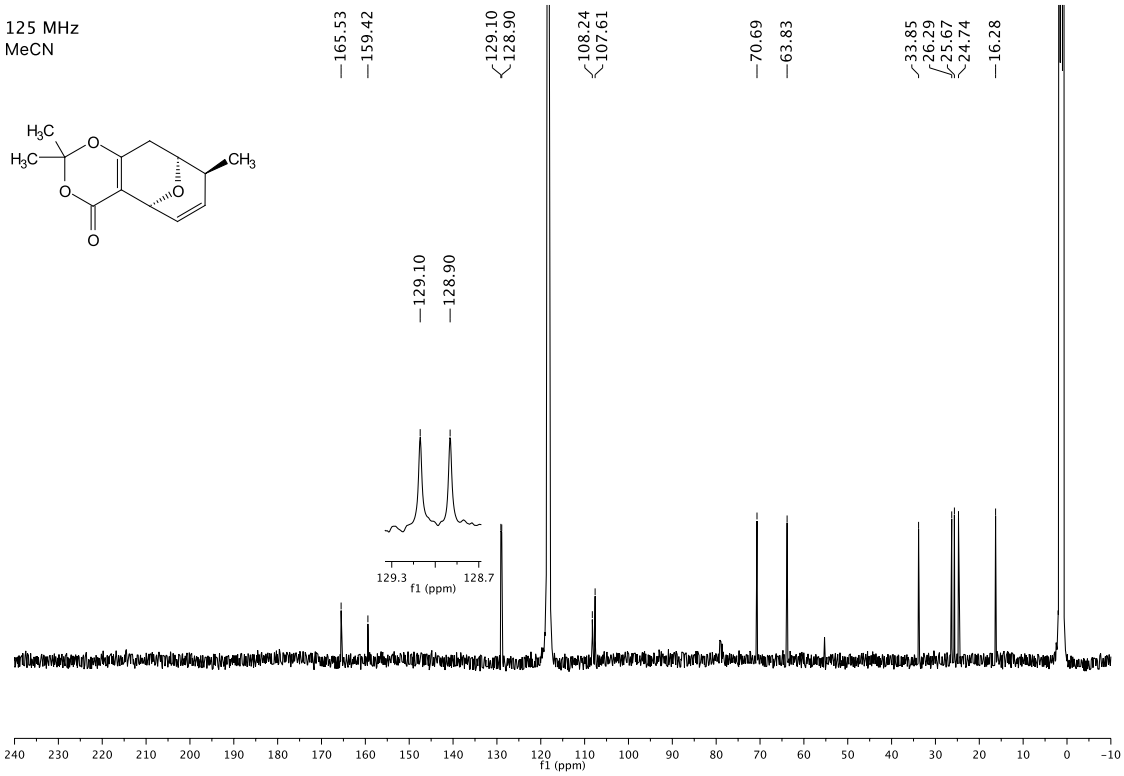


((3R,4R,5S,E)-6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-4-methyl-3,5-bis((triethylsilyl)oxy)hex-1-en-1-yl)(phenyl)iodonium trifluoromethanesulfonate **531**



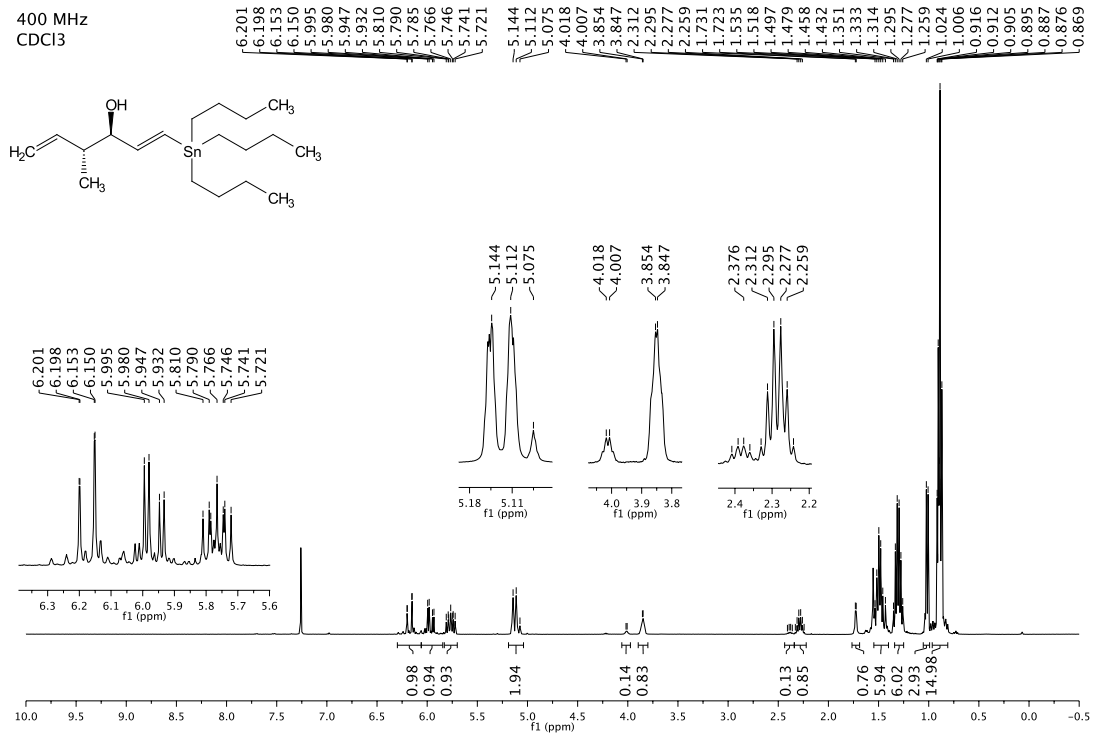
(5S,8S,9S)-2,2,8-trimethyl-5,8,9,10-tetrahydro-4H-5,9-epoxycycloocta[d][1,3]dioxin-4-one **552**

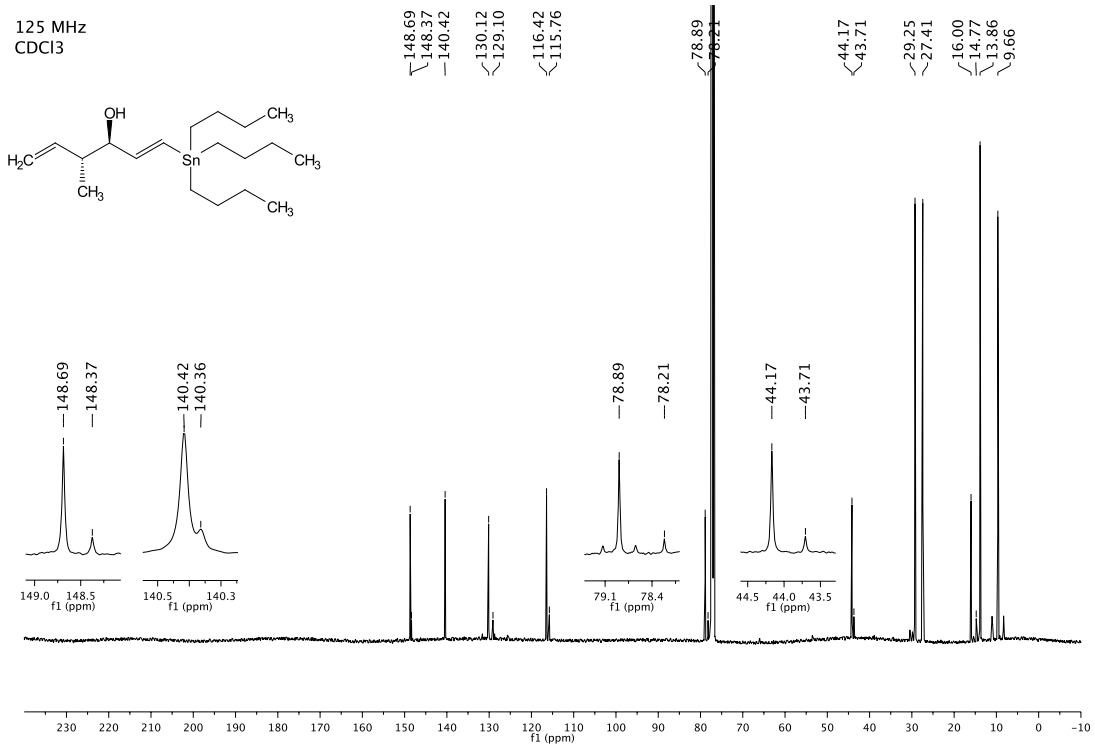




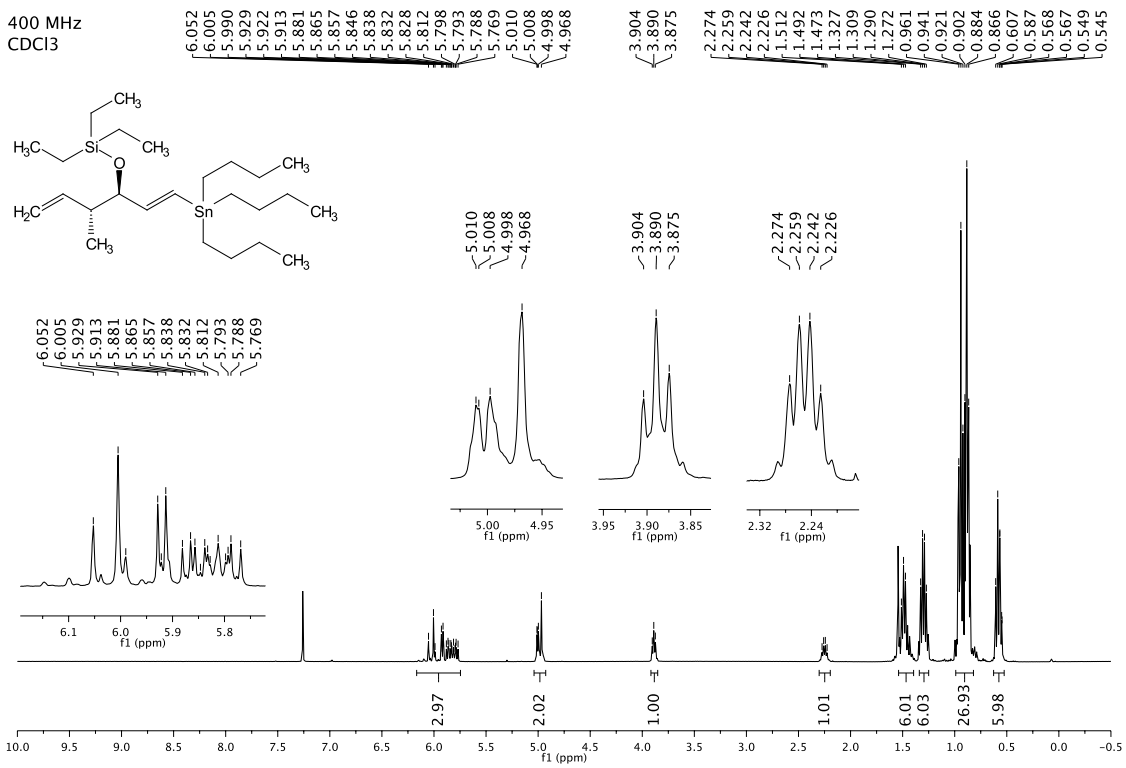
viii.2.4 Third generation

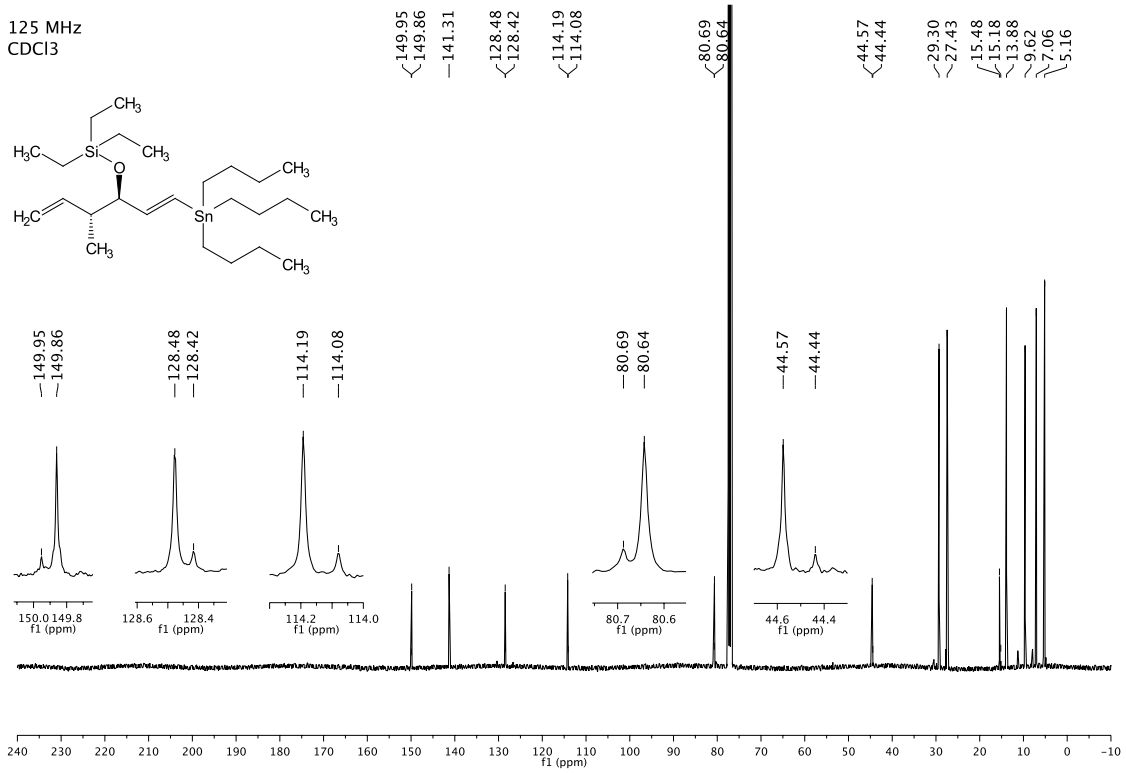
(3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-ol **563**



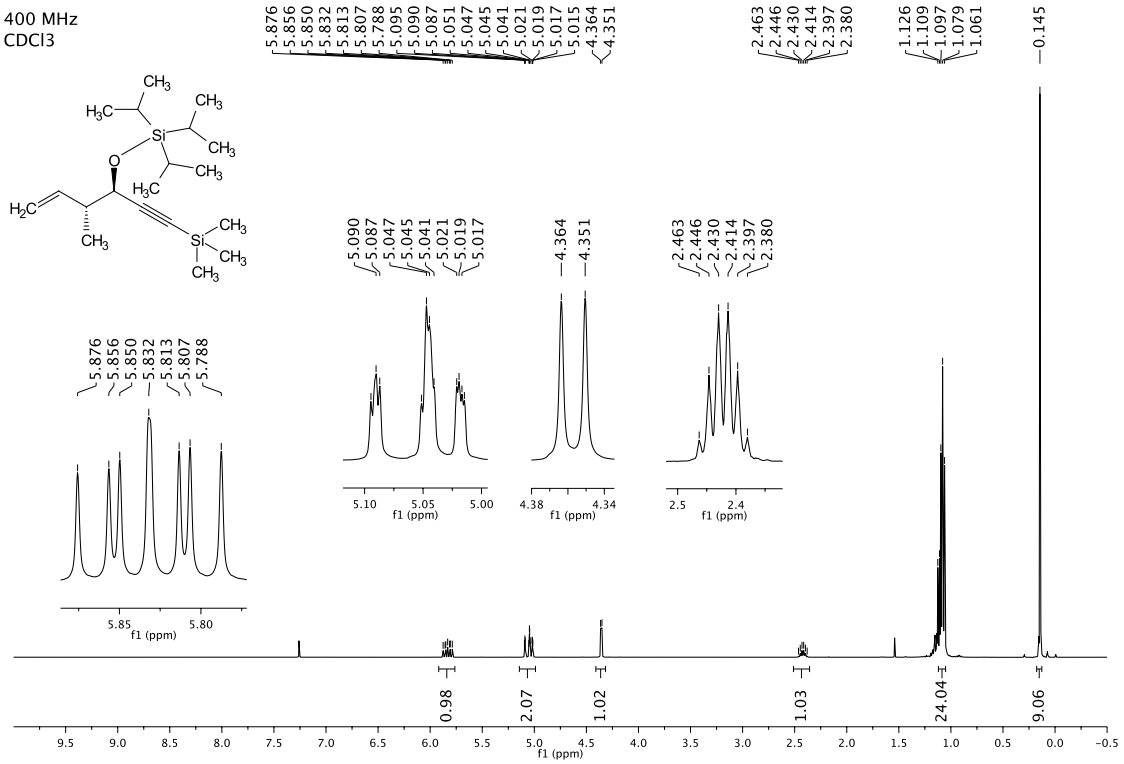


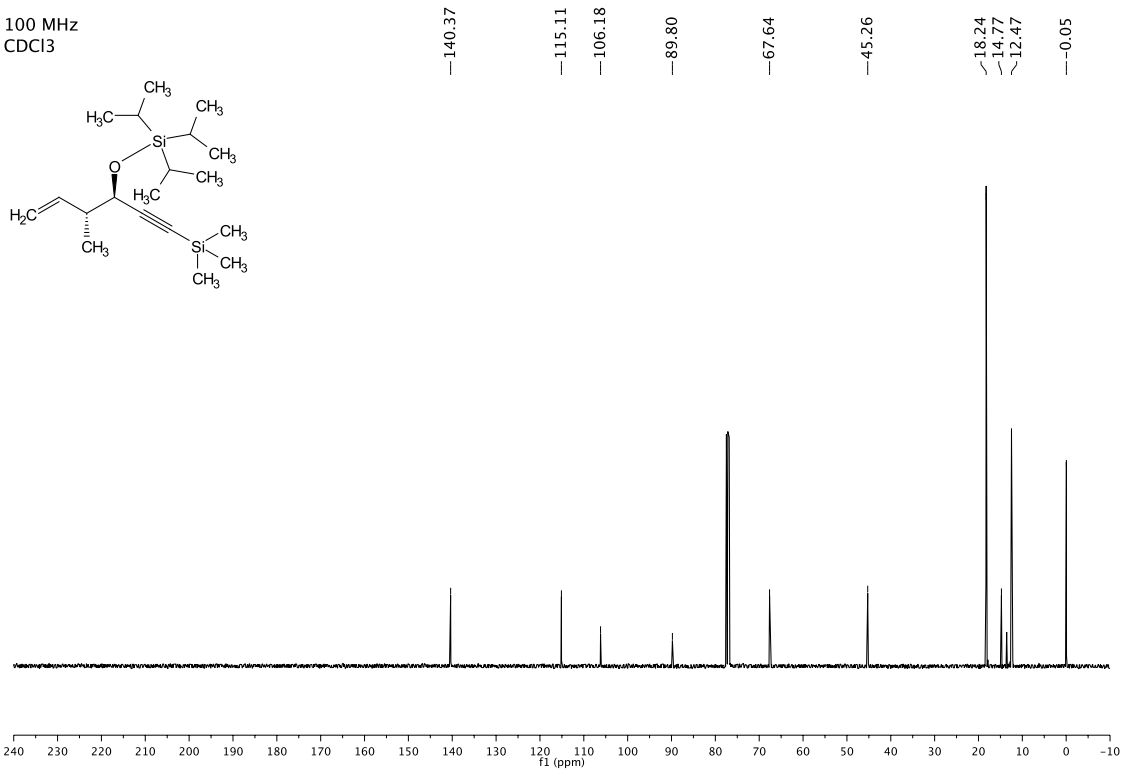
triethyl(((3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-yl)oxy)silane **563**



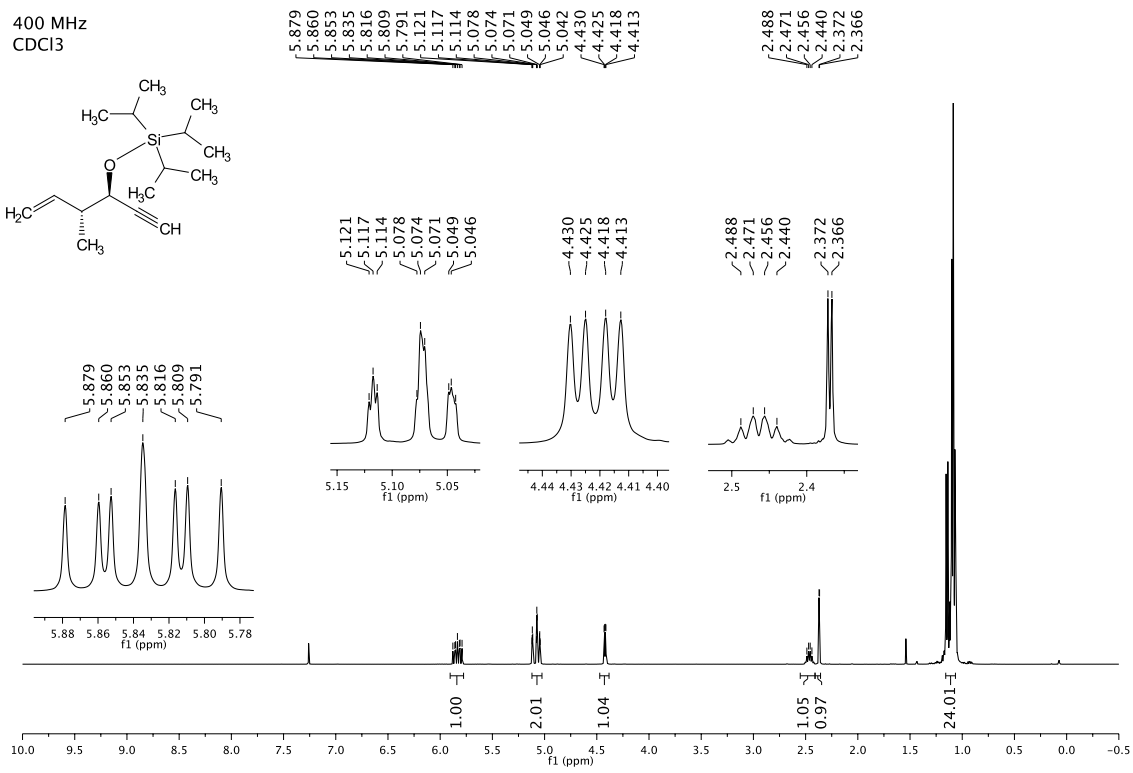


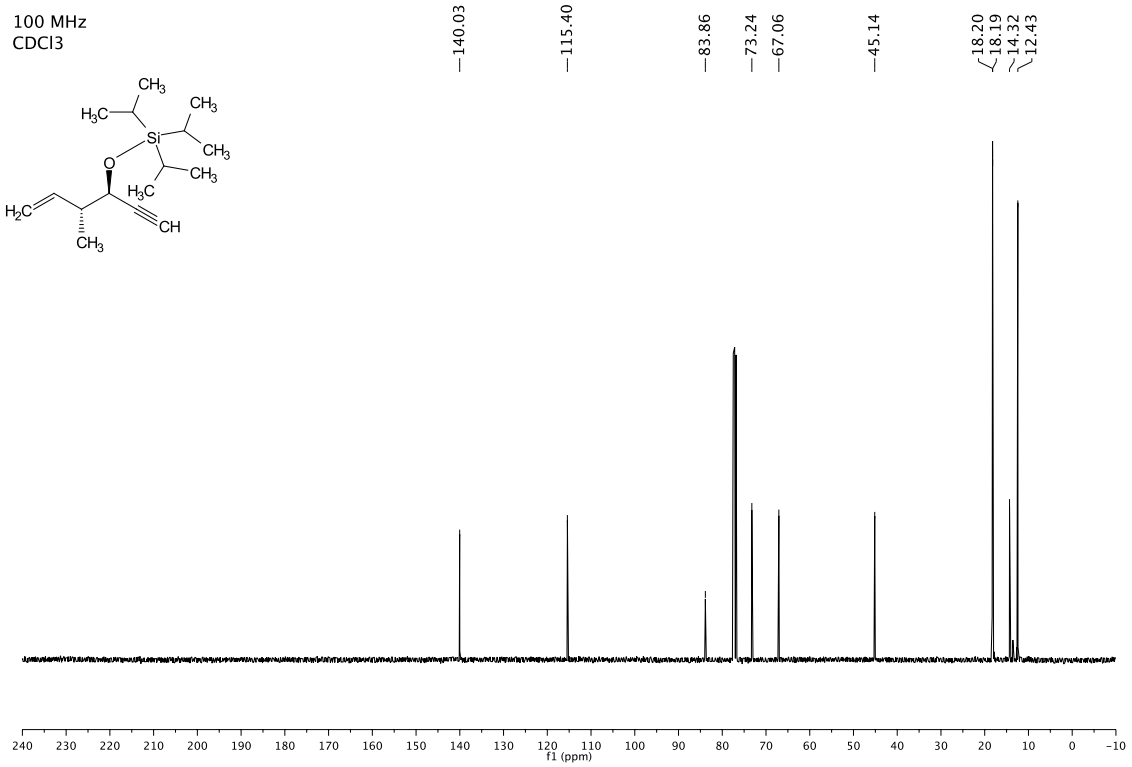
triisopropyl(((3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-yl)oxy)silane **565**



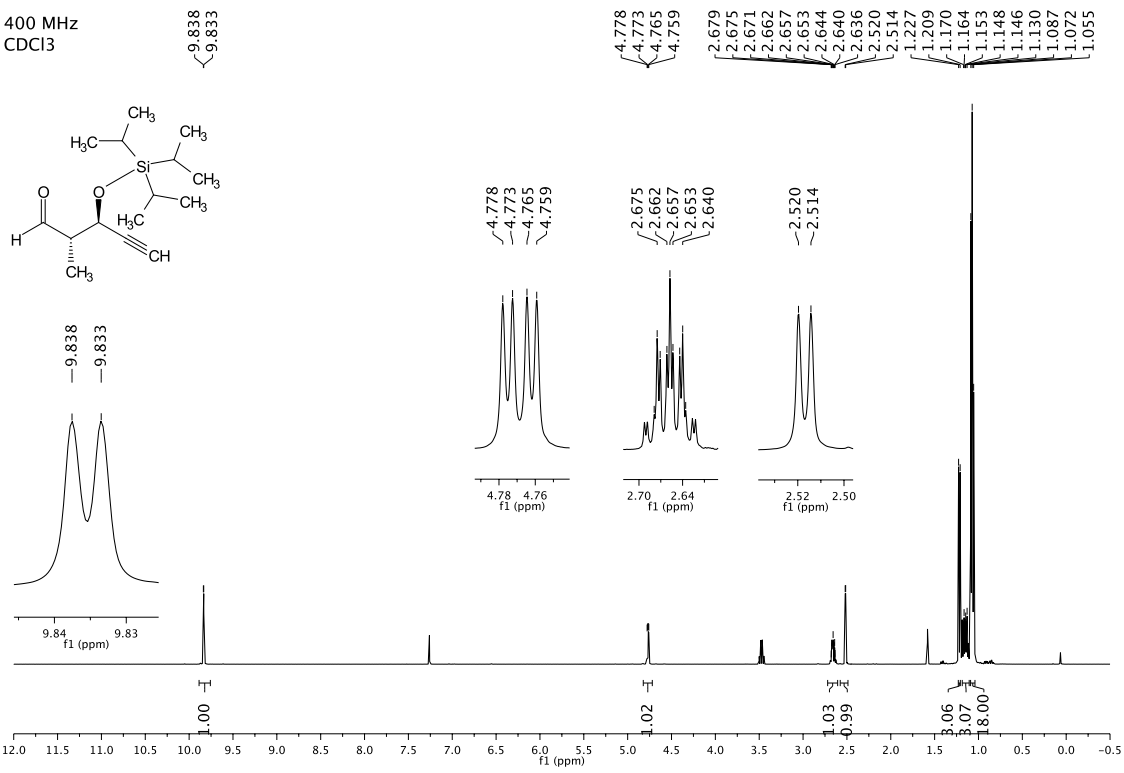


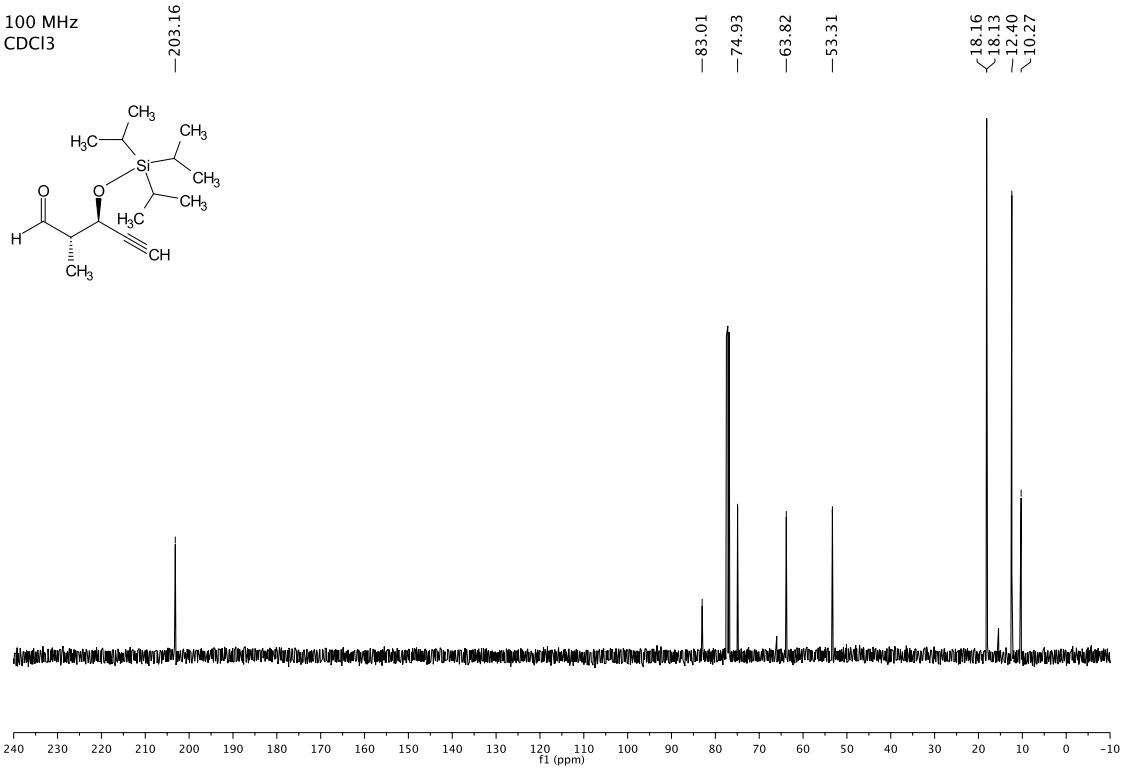
triisopropyl(((3R,4R)-4-methylhex-5-en-1-yn-3-yl)oxy)silane **566**



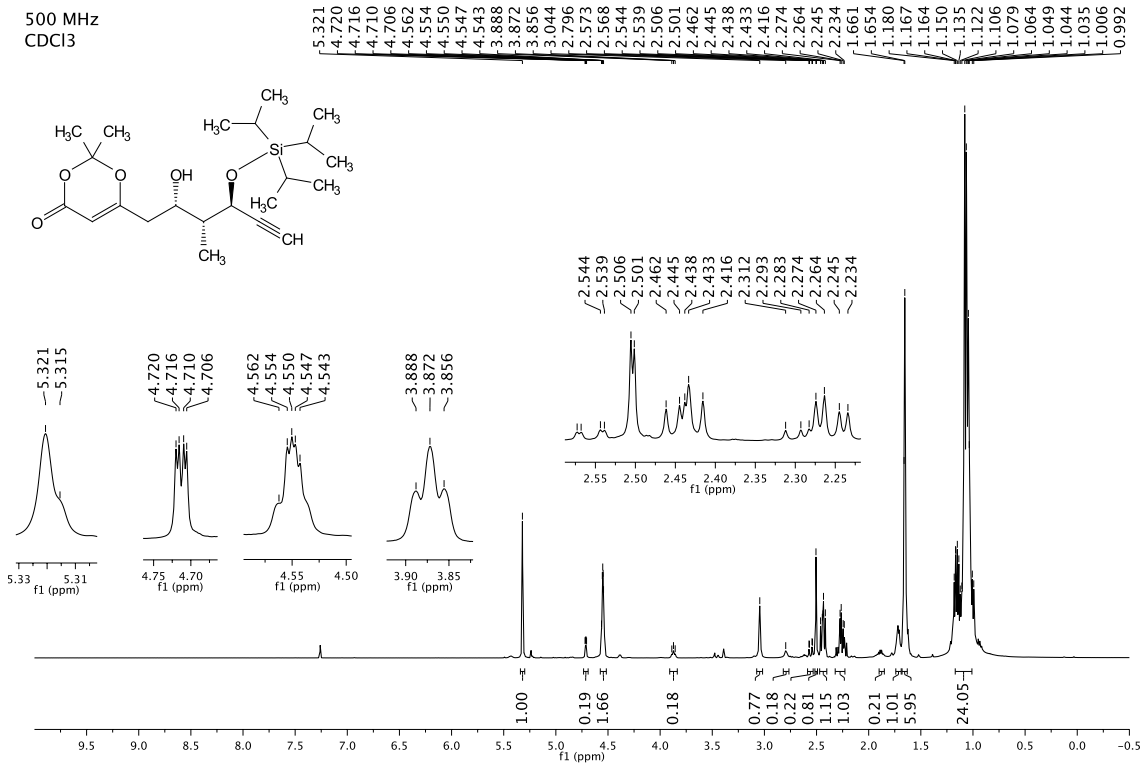


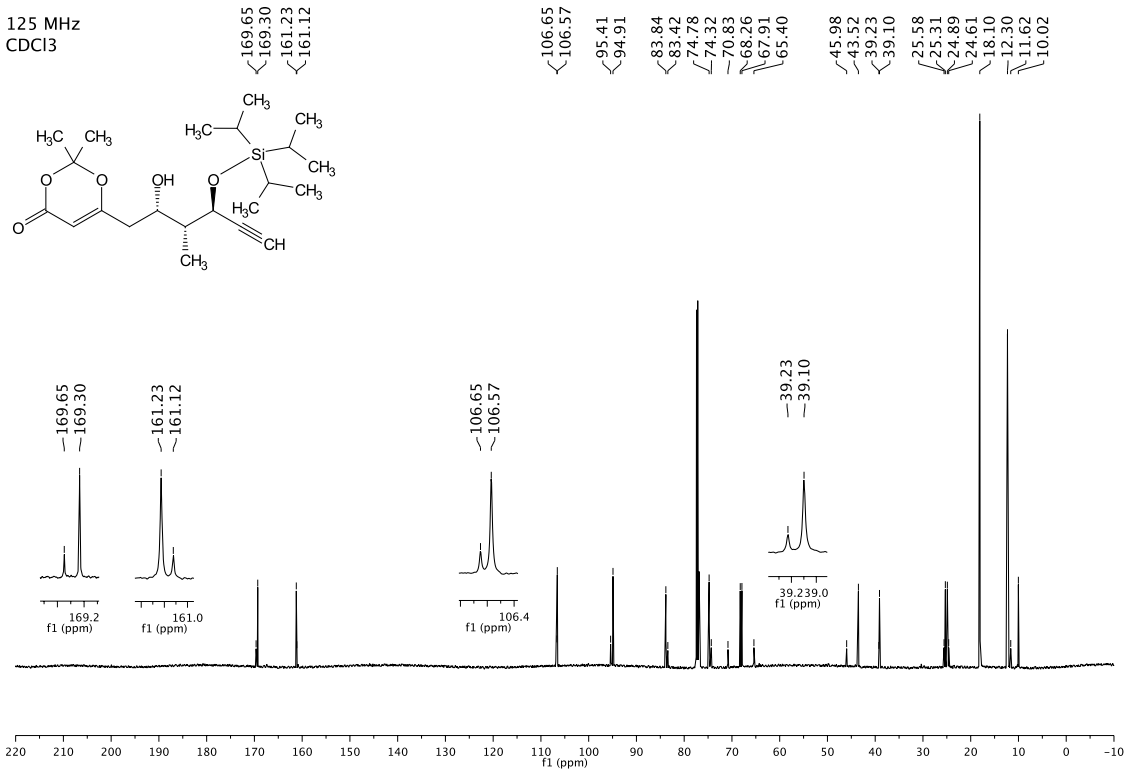
(2S,3R)-2-methyl-3-((triisopropylsilyl)oxy)pent-4-ynal **567**



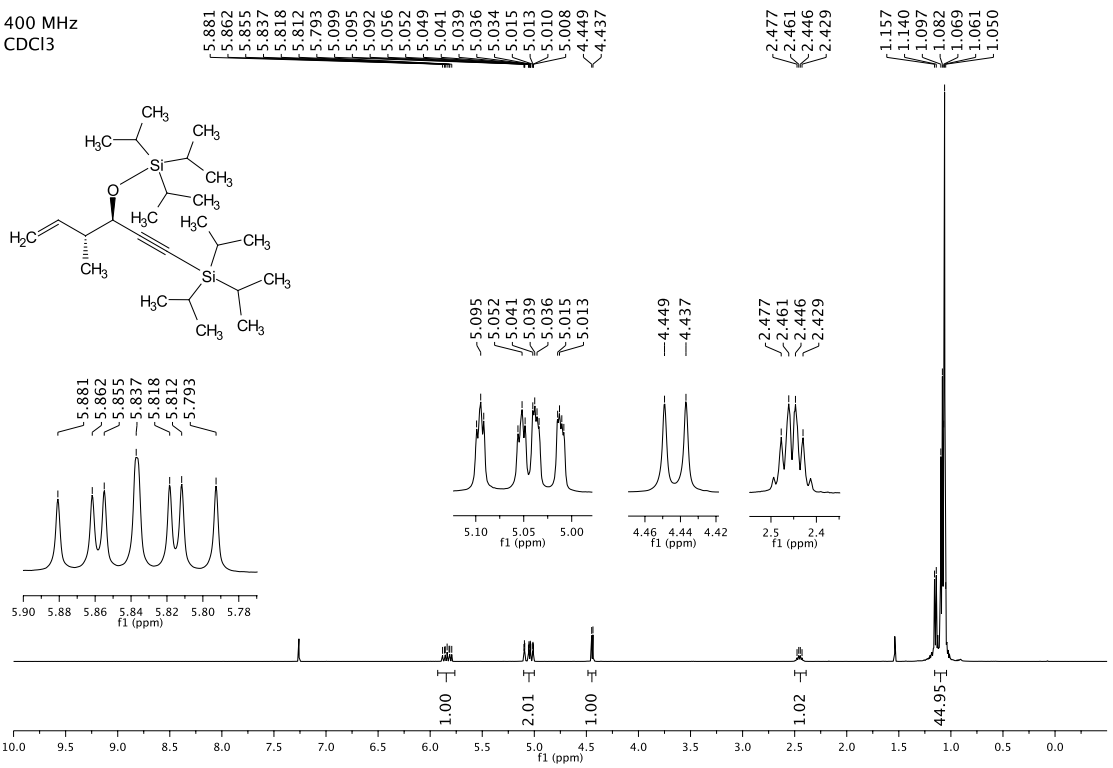


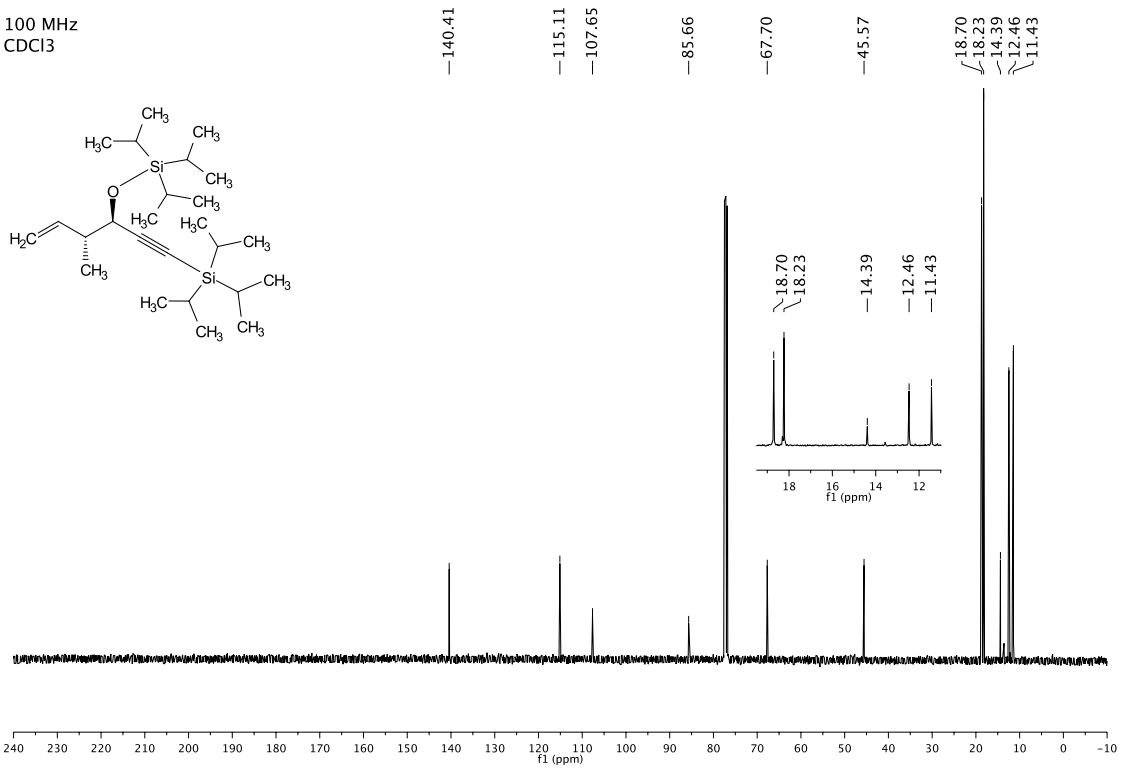
6-((2S,3R,4R)-2-hydroxy-3-methyl-4-((triisopropylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **568**



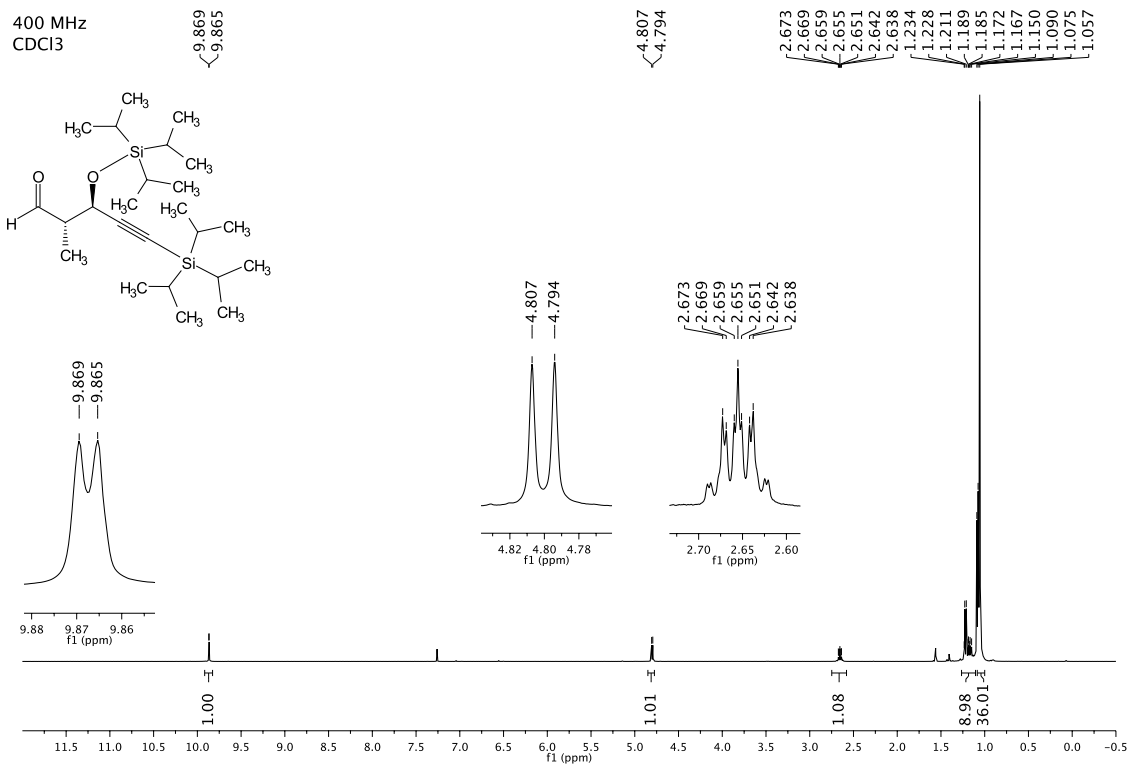


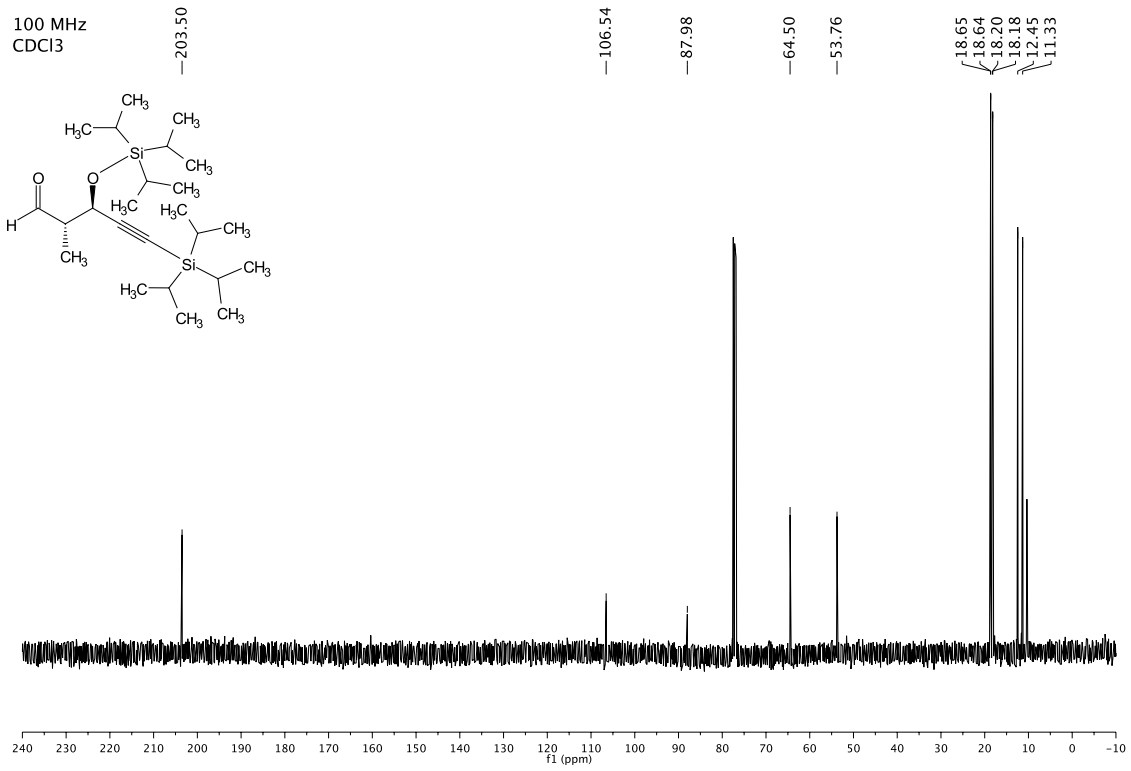
triisopropyl(((3R,4R)-4-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl)oxy)silane **569**



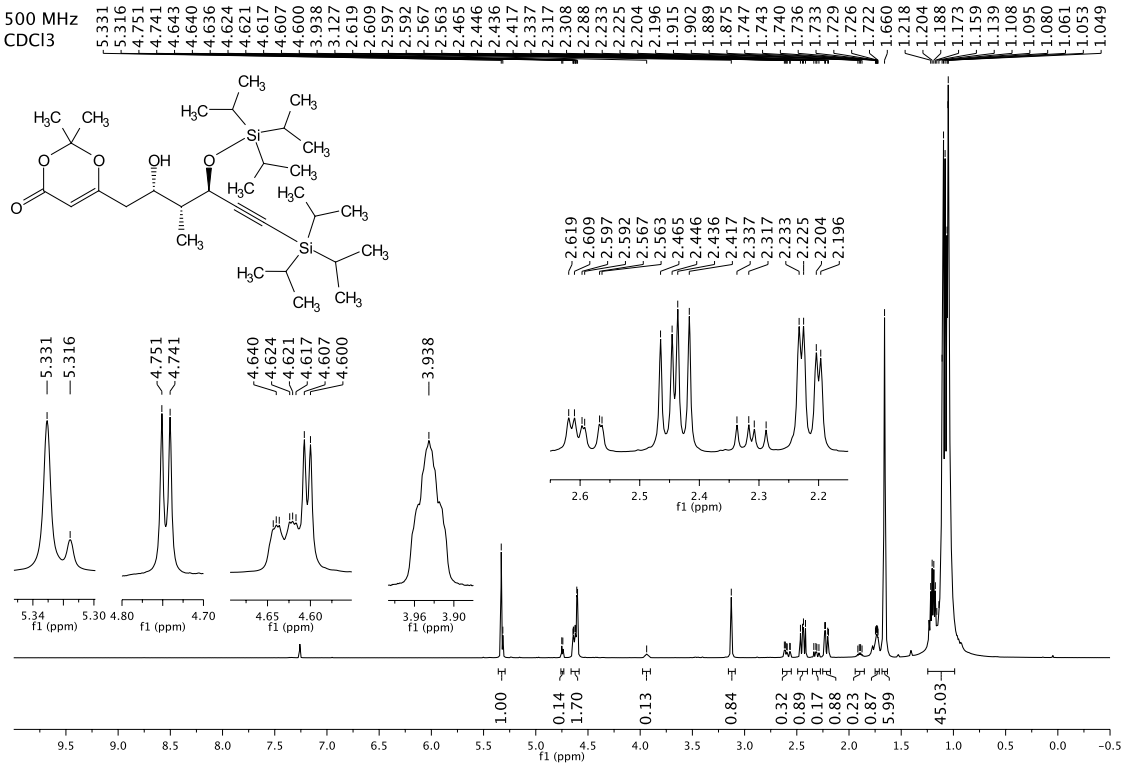


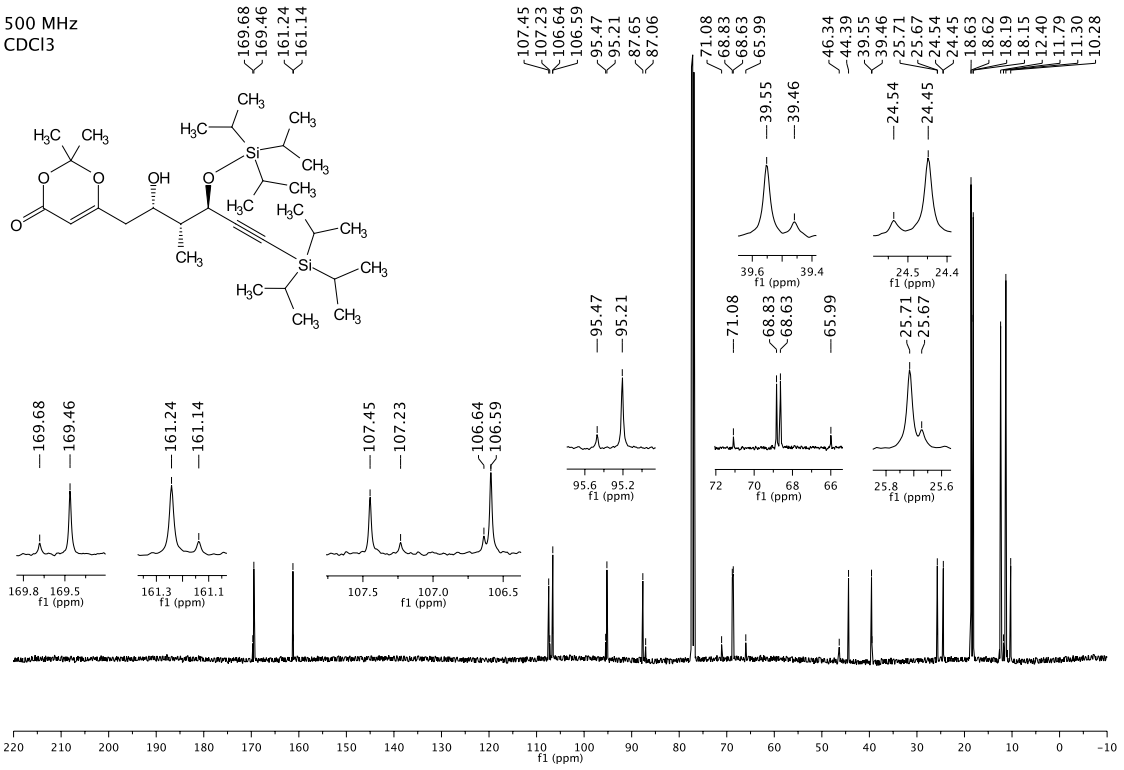
(2S,3R)-2-methyl-5-(triisopropylsilyl)-3-((triisopropylsilyl)oxy)pent-4-ynal **570**



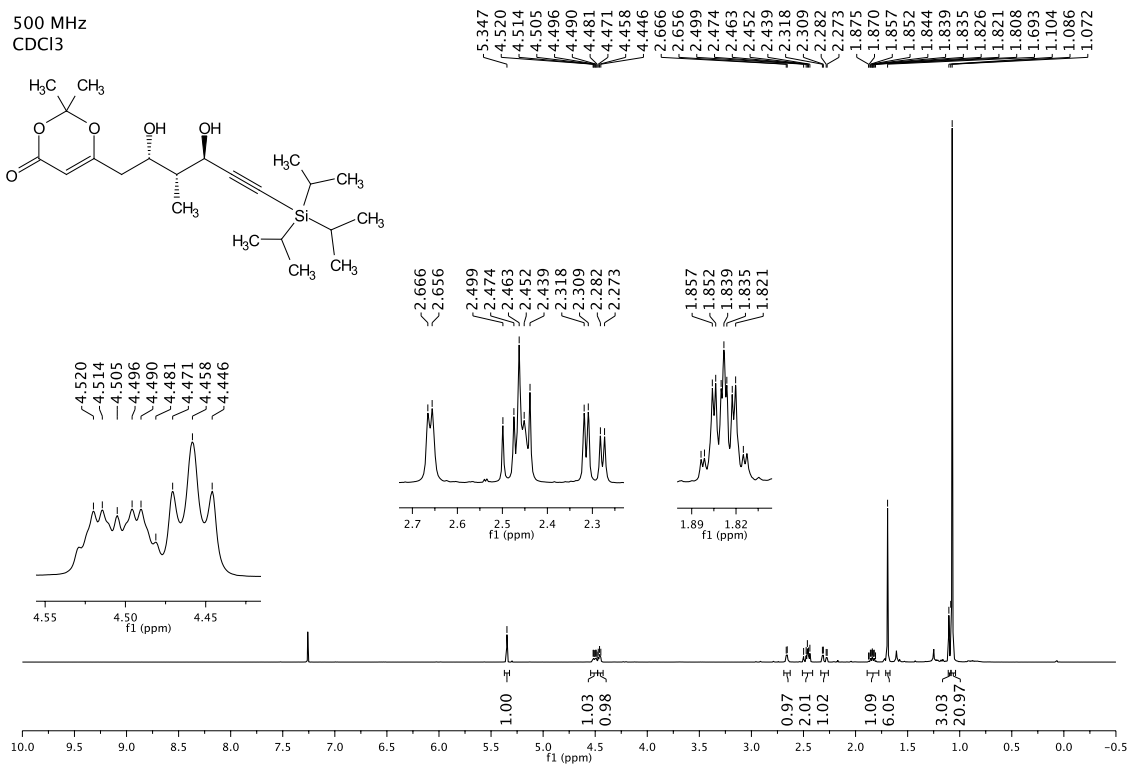


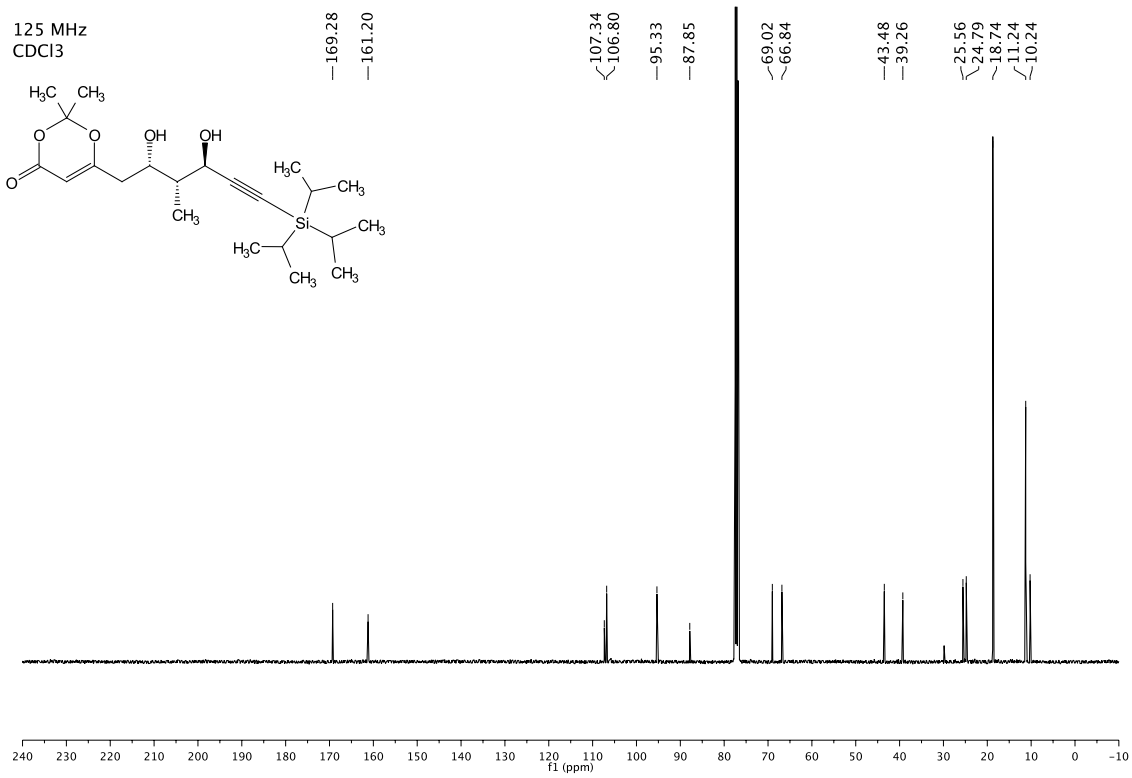
6-((2S,3R,4R)-2-hydroxy-3-methyl-6-(triisopropylsilyl)-4-((triisopropylsilyl)oxy)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **571**



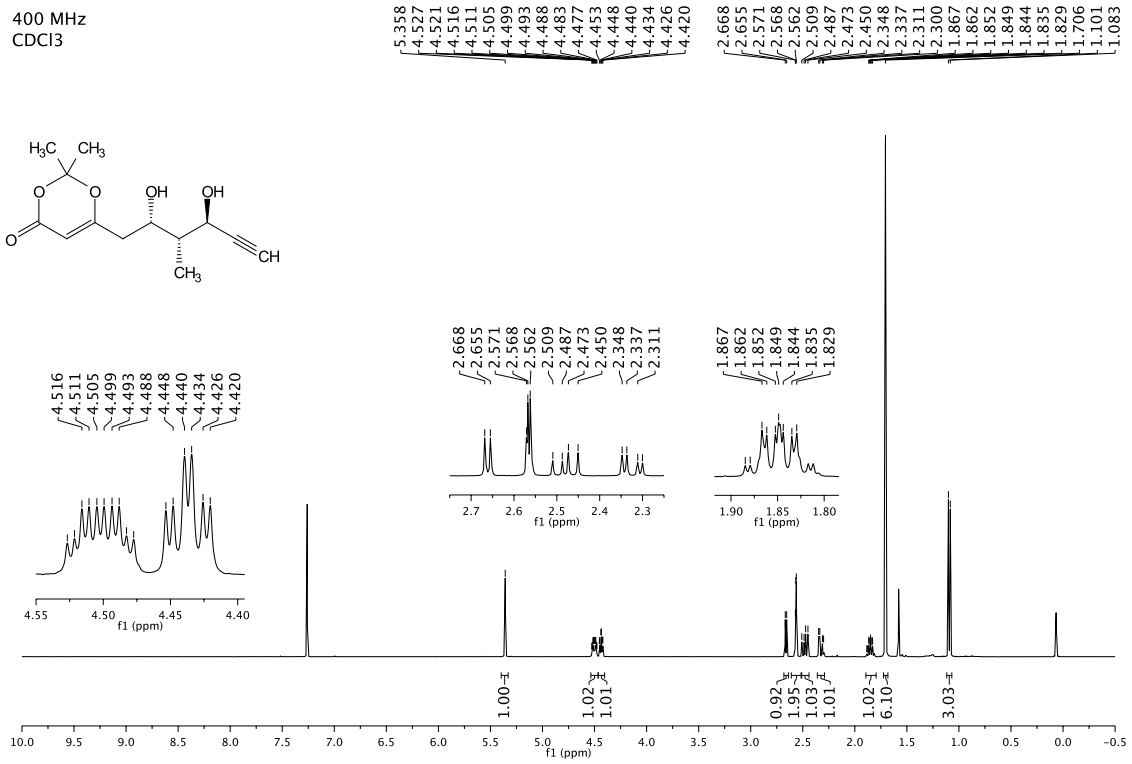


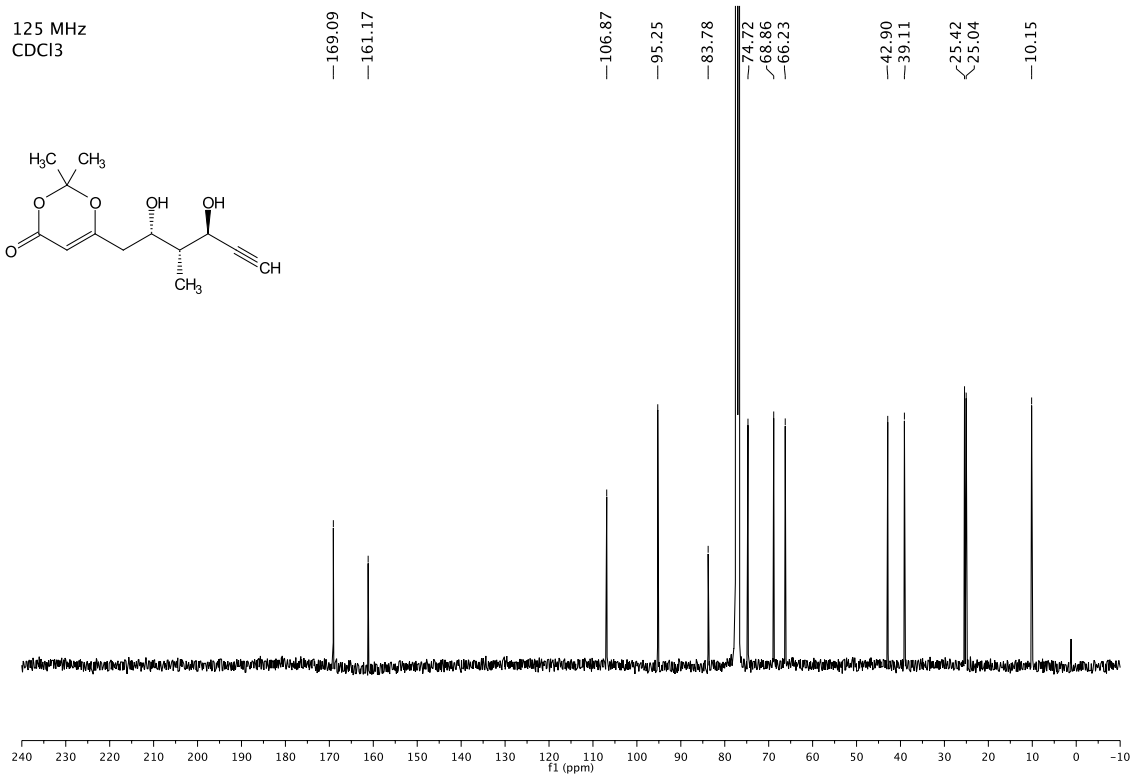
6-((2S,3R,4R)-2,4-dihydroxy-3-methyl-6-(triisopropylsilyl)hex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **573**



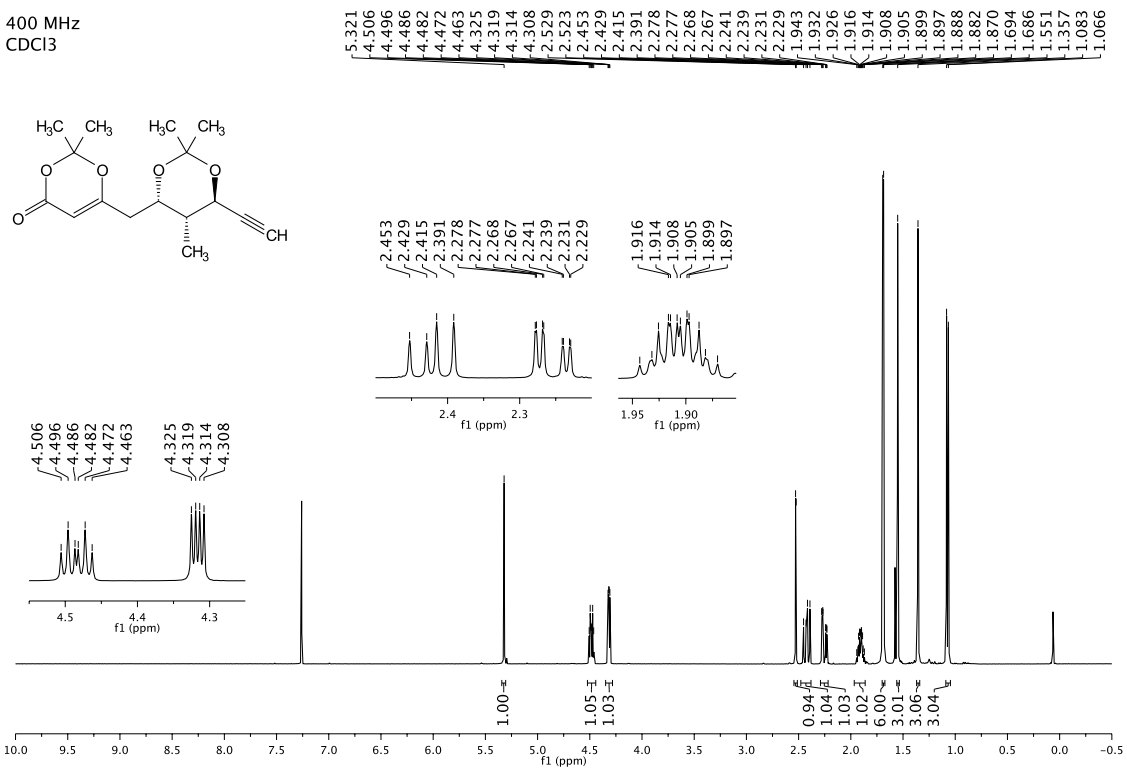


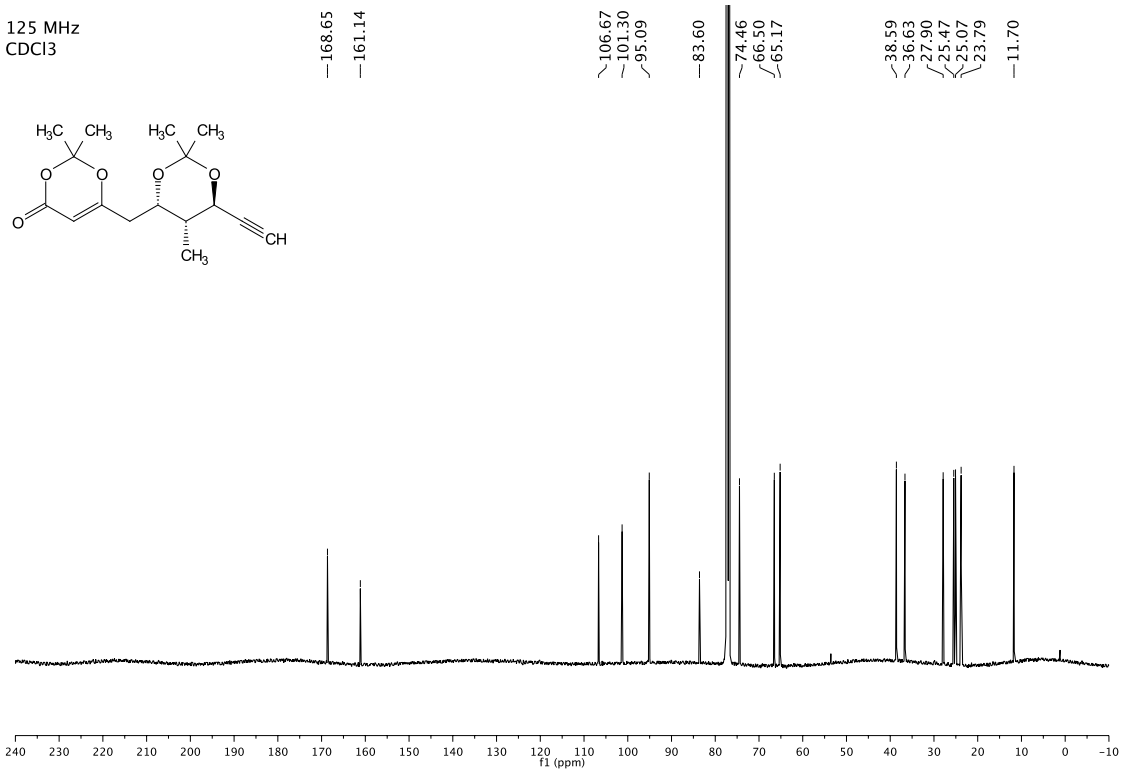
6-((2S,3R,4R)-2,4-dihydroxy-3-methylhex-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one **572**



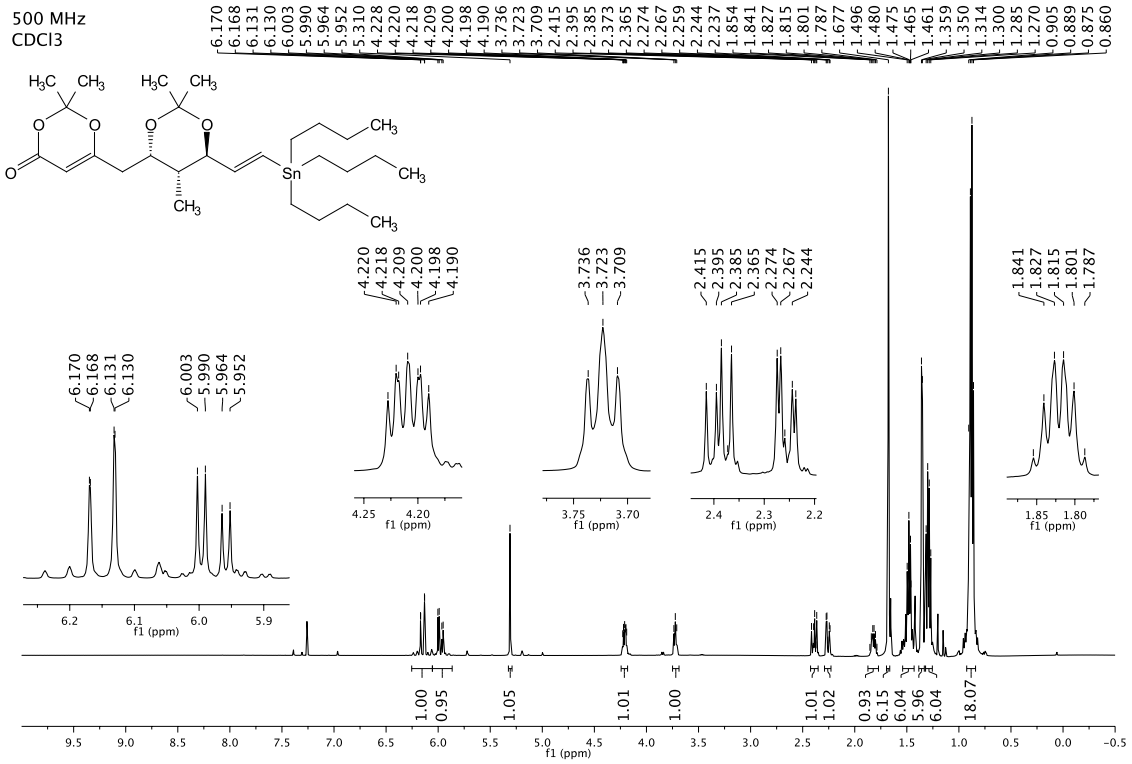


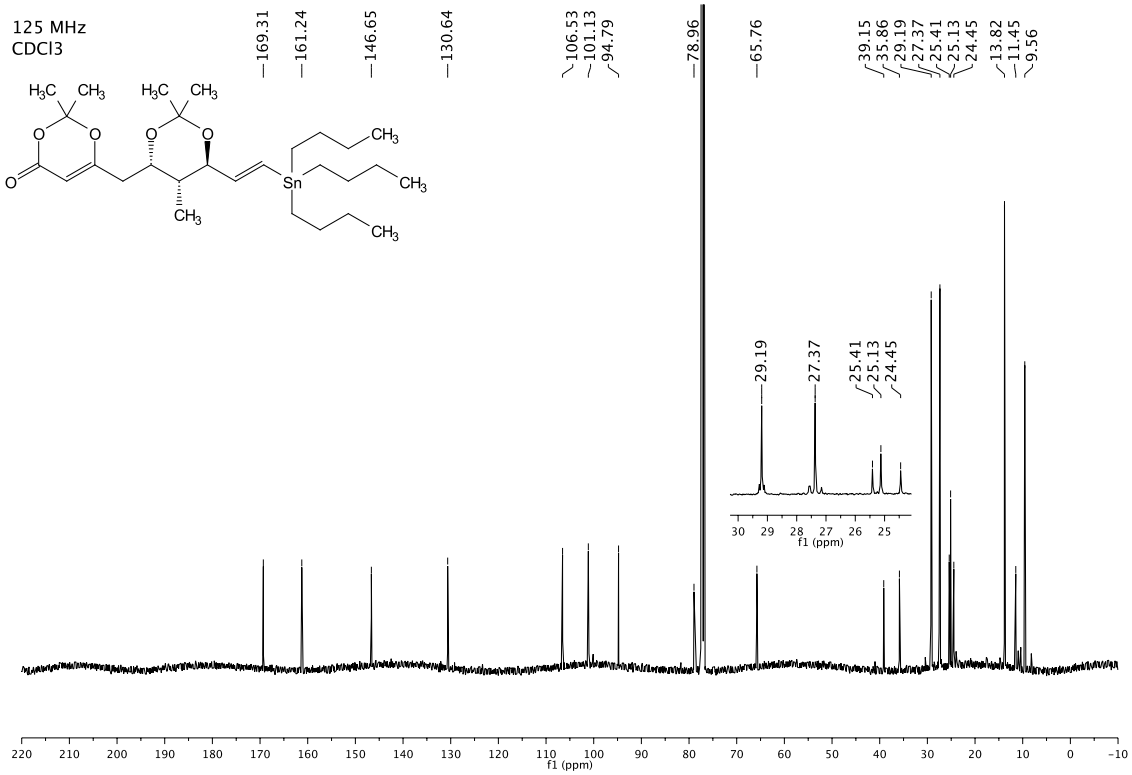
6-(((4S,5R,6R)-6-ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **574**



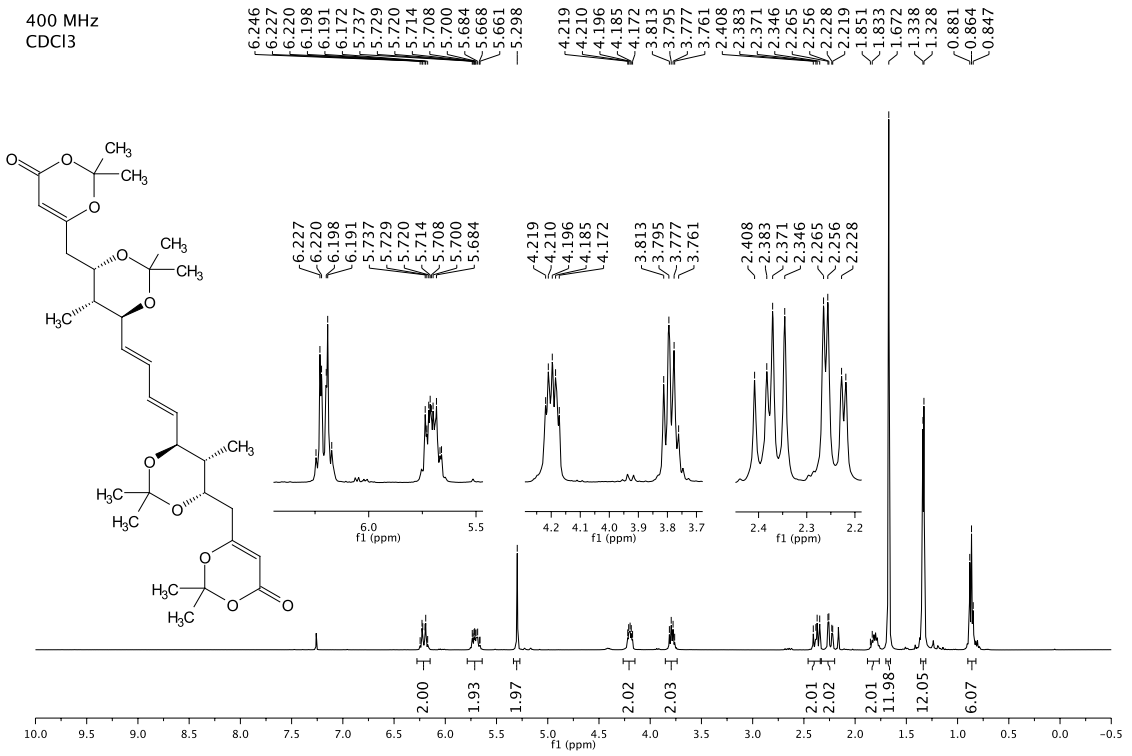


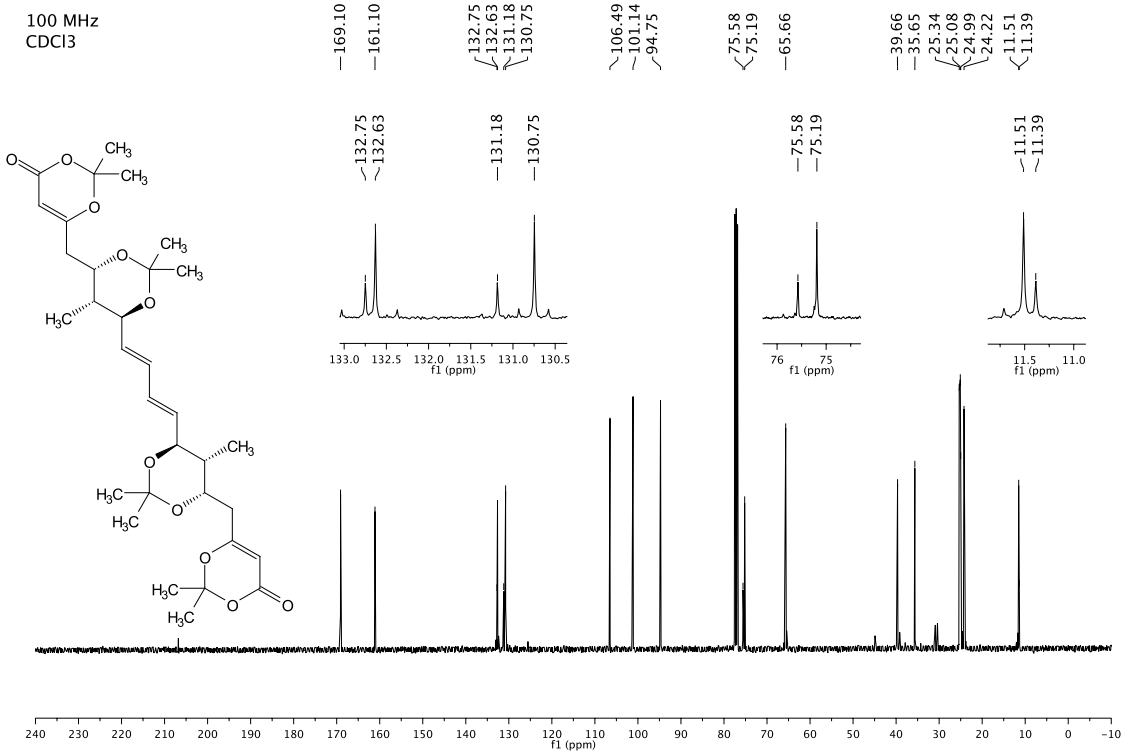
2,2-dimethyl-6-(((4S,5R,6R)-2,2,5-trimethyl-6-((E)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)methyl)-4H-1,3-dioxin-4-one **560**



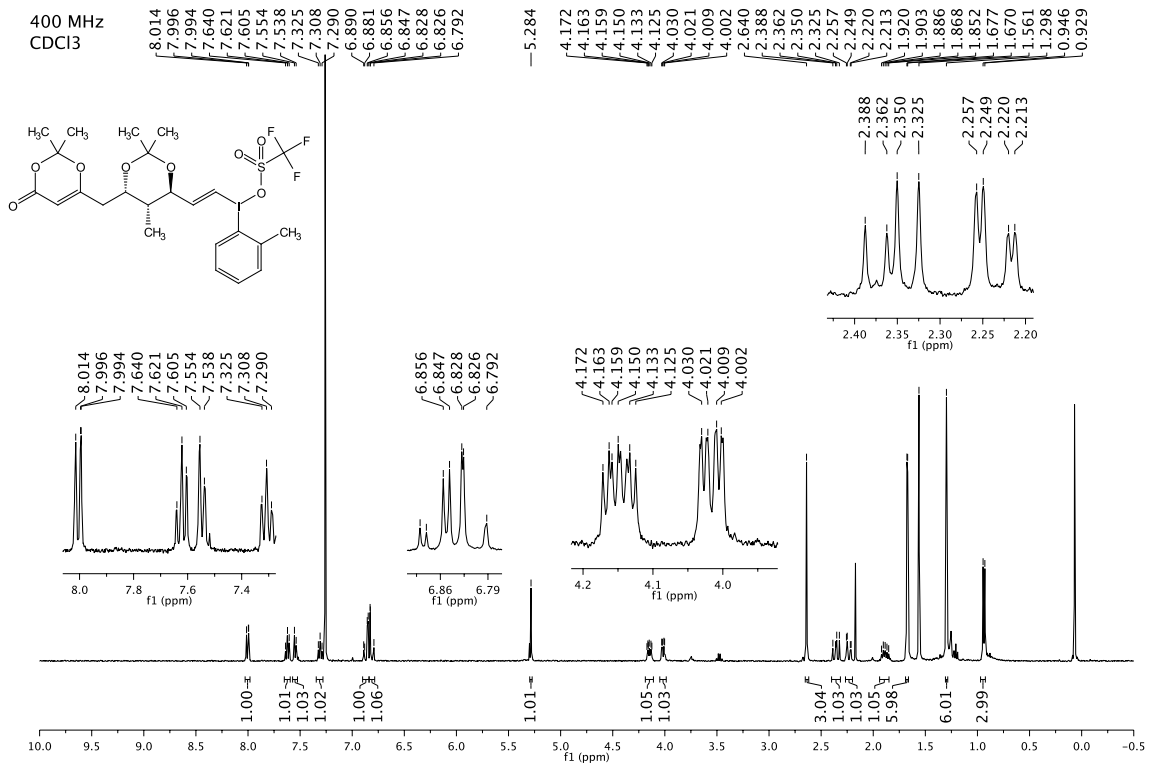


6,6'-(((4S,4'S,5R,5'R,6S,6'S)-((1E,3E)-buta-1,3-diene-1,4-diyl)bis(2,2,5-trimethyl-1,3-dioxane-6,4-diyl))bis(methylene))bis(2,2-dimethyl-4H-1,3-dioxin-4-one) **575**

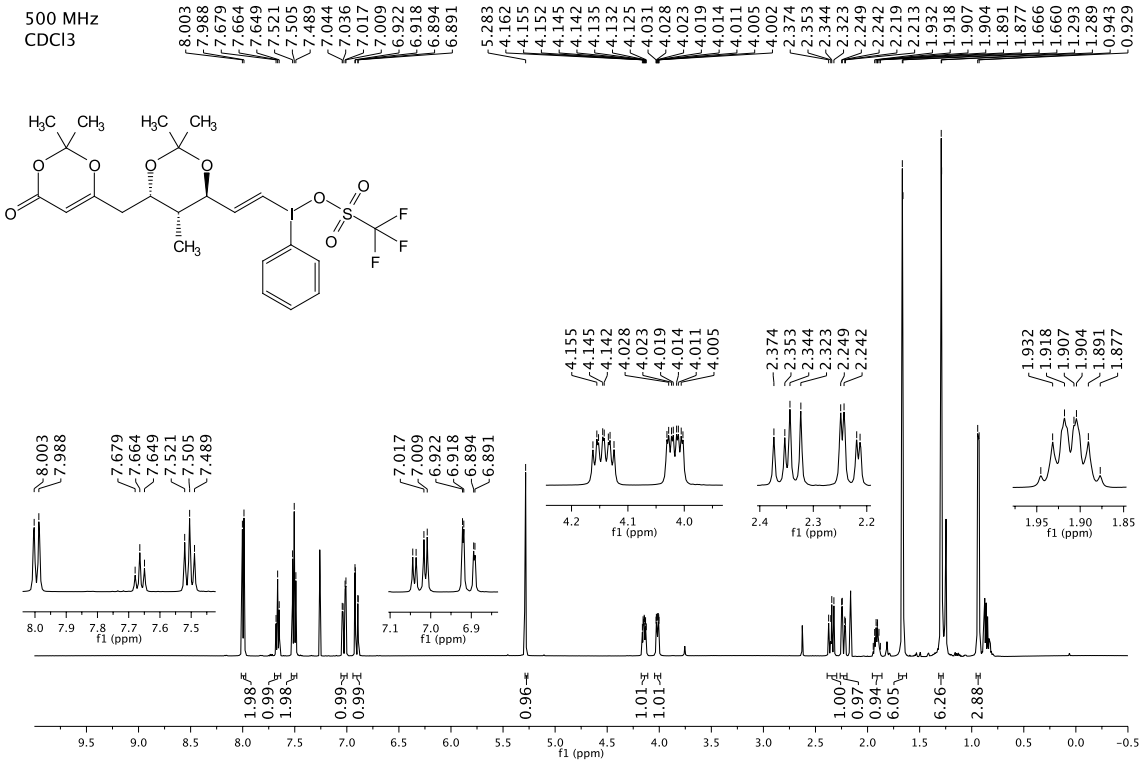


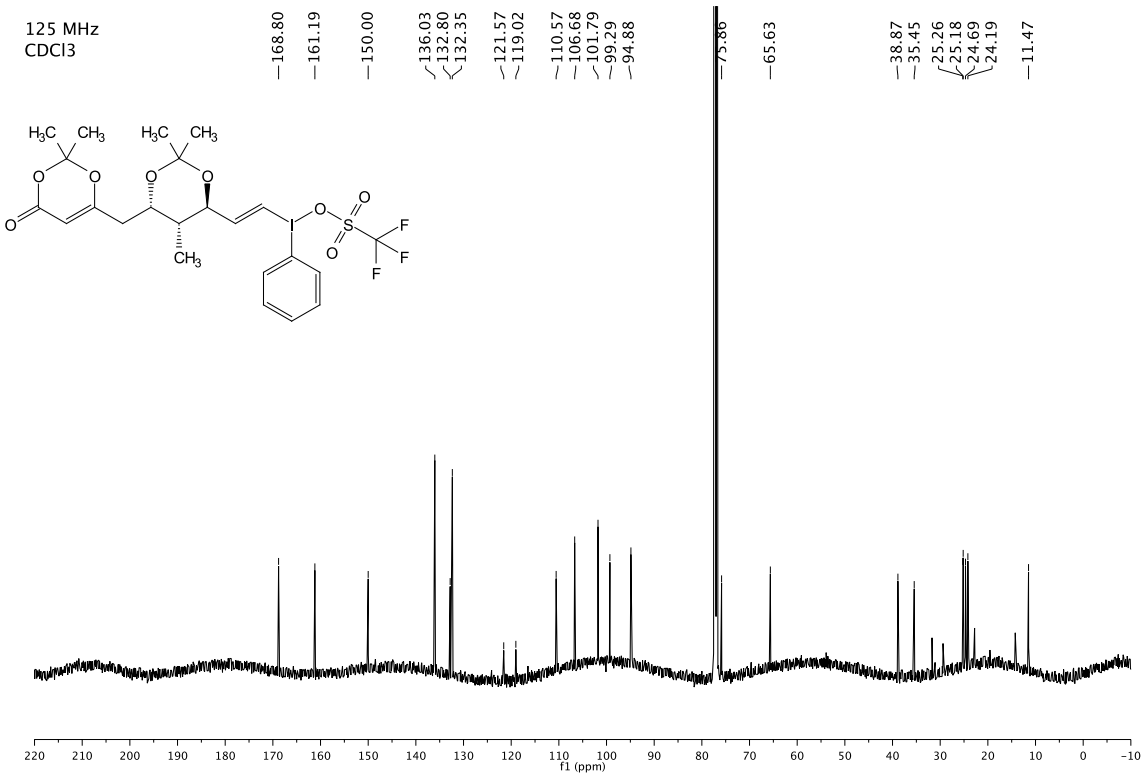


((E)-2-((4R,5R,6S)-6-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)vinyl)(o-tolyl)-iodonium trifluoromethanesulfonate **577**

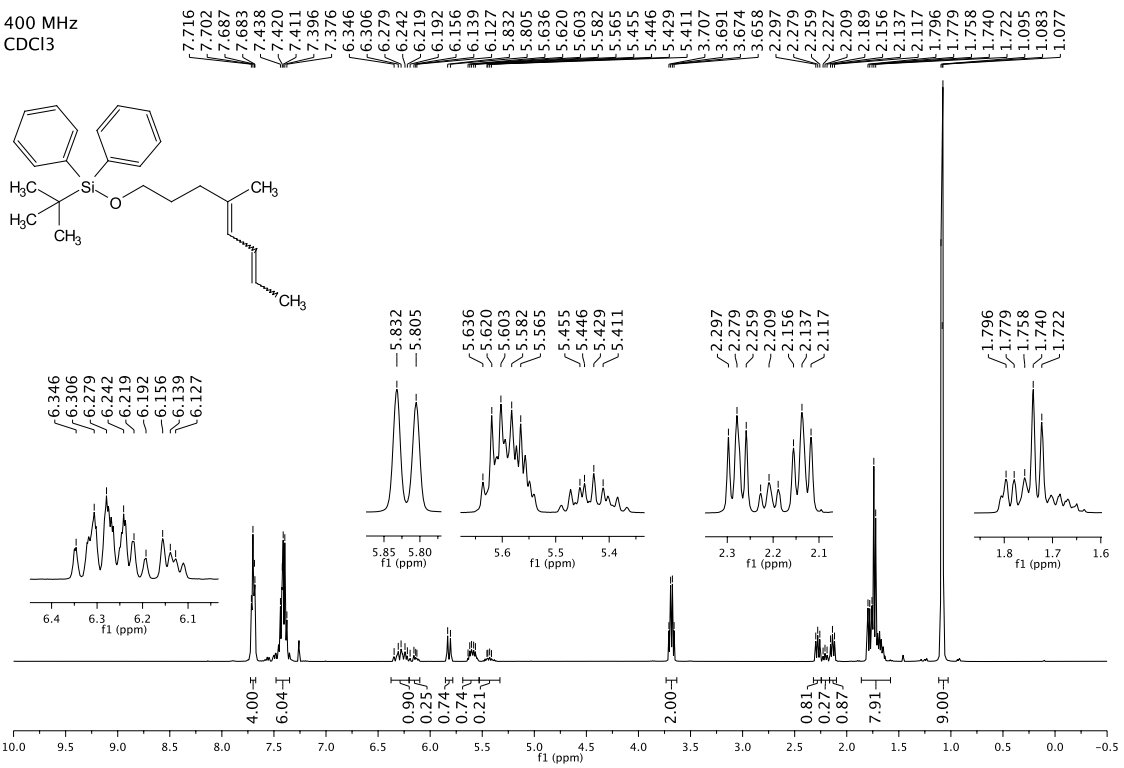


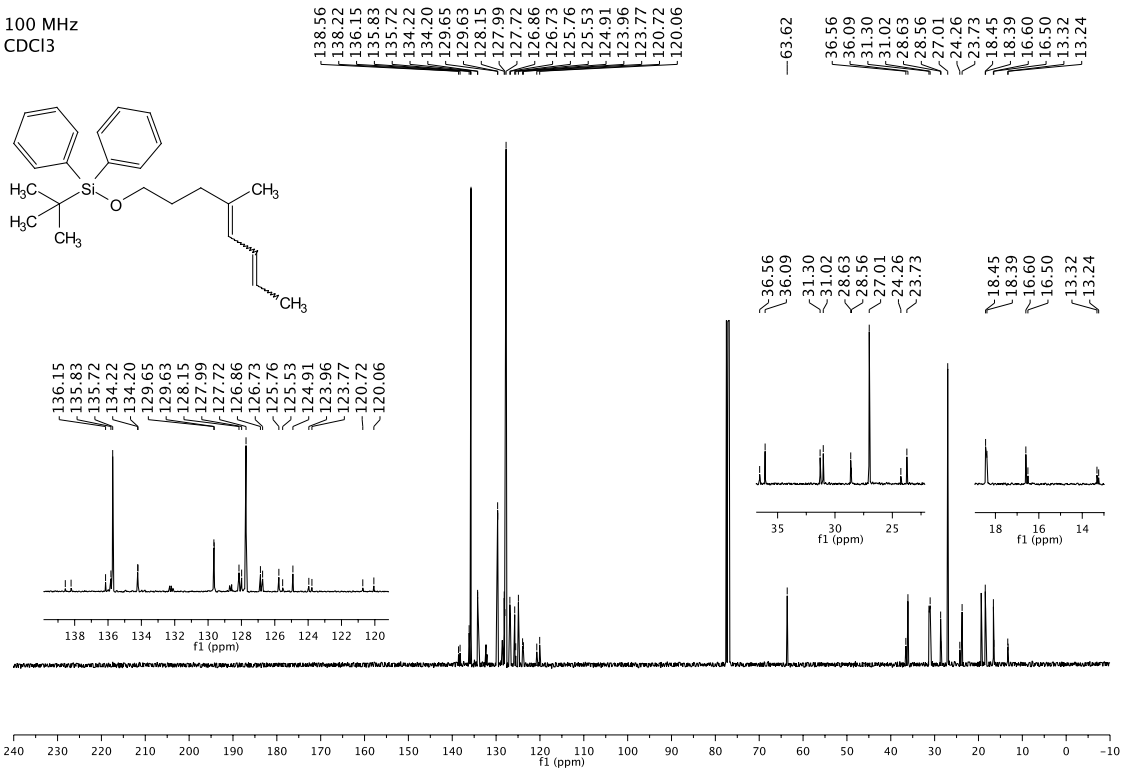
((E)-2-((4R,5R,6S)-6-((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)vinyl)(phenyl)-iodonium trifluoromethanesulfonate **558**



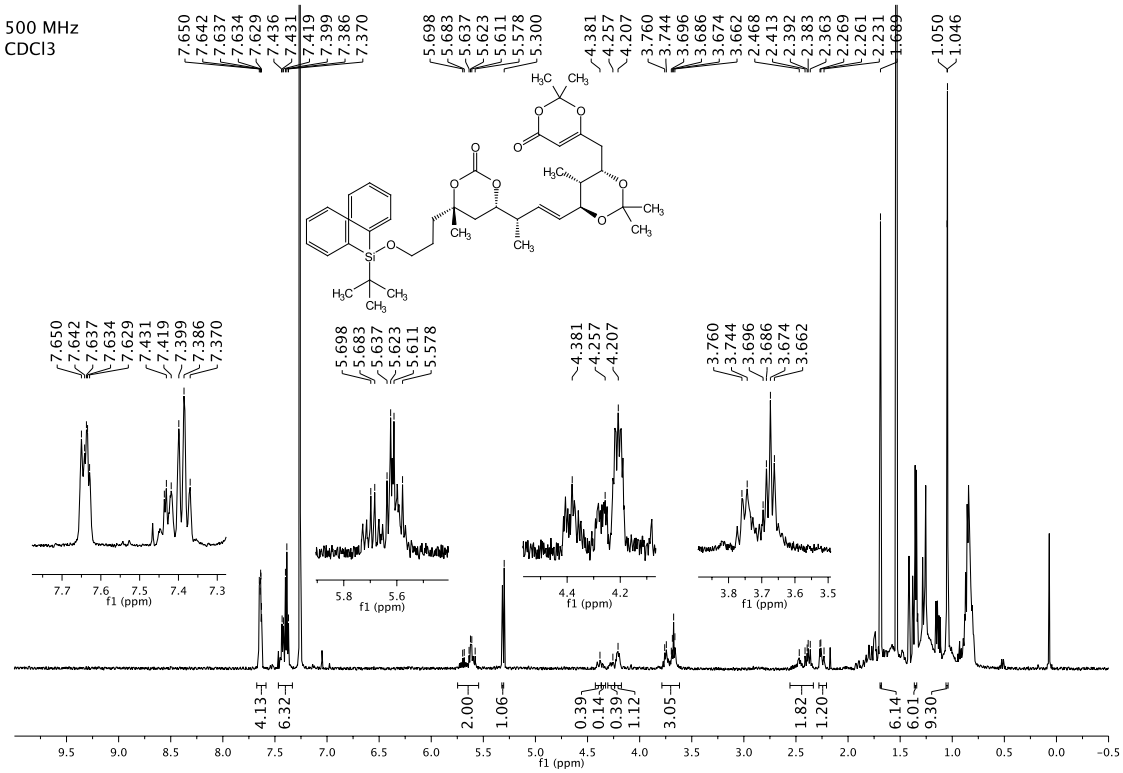


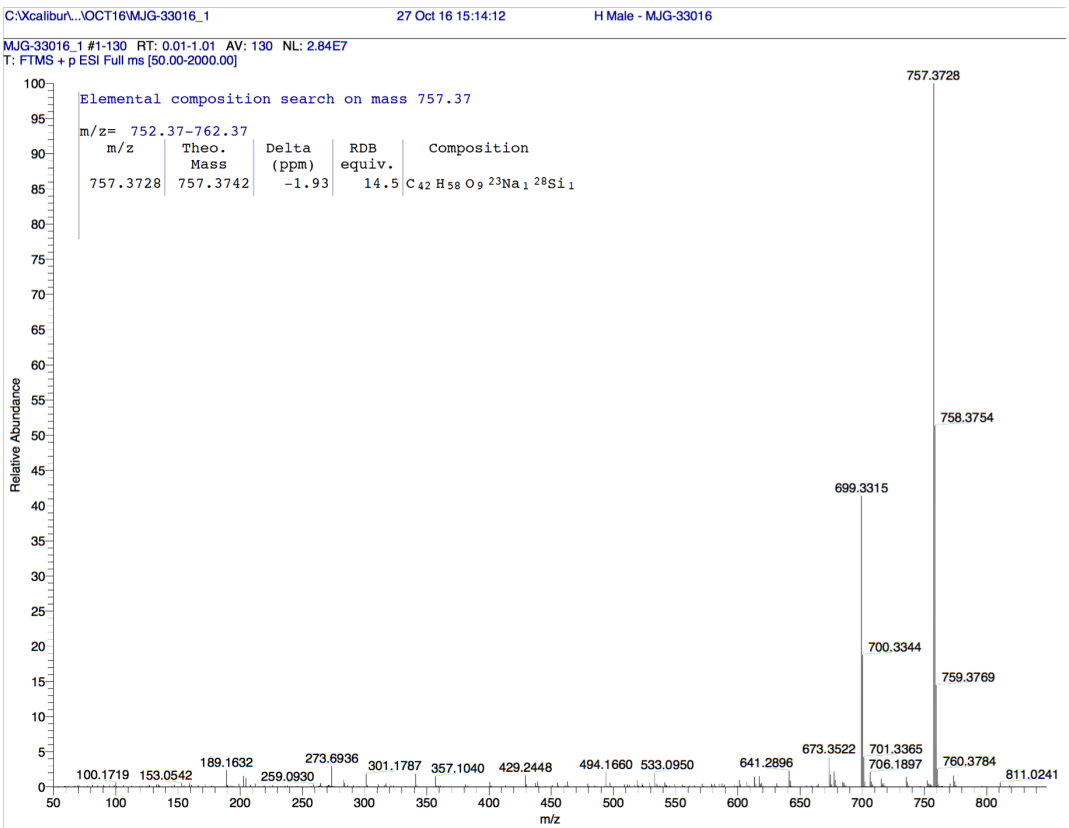
tert-butyl(((4E,6E)-4-methylocta-4,6-dien-1-yl)oxy)diphenylsilane **584**





6-(((4S,5R,6S)-6-((S,E)-3-((4S,6S)-6-(3-((tert-butyldiphenylsilyl)oxy)propyl)-6-methyl-2-oxo-1,3-dioxan-4-yl)but-1-en-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **591**



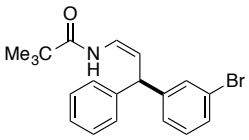


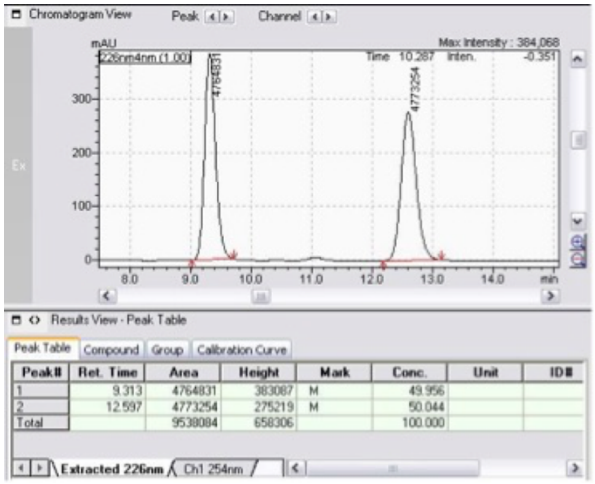
ix Appendix 3 – Chiral HPLC and GC-FID Traces

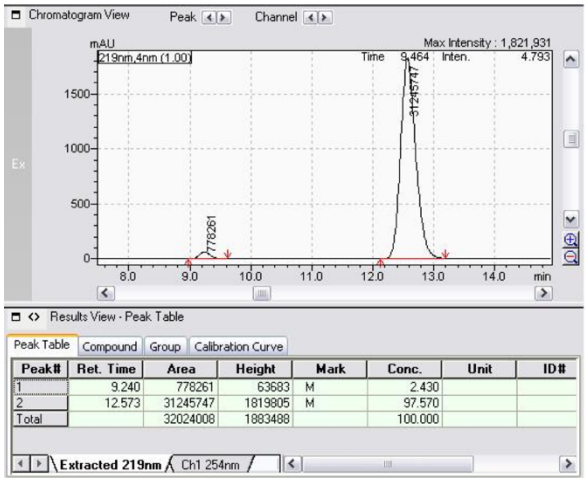
viii.1 The Enantioselective and Regiodivergent Copper-Catalysed Arylation of Allylic Amides with Diaryliodonium Salts

viii.1.1 Enamide products and derivatives

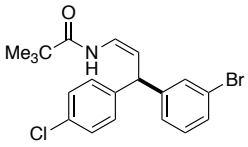
(R)-N-[(1Z)-3-(3-bromophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **332**

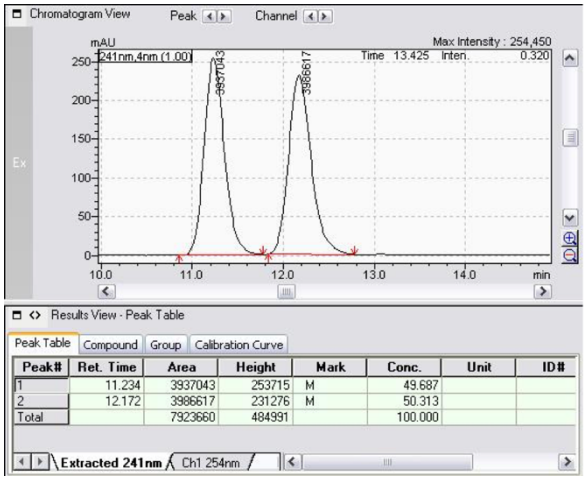


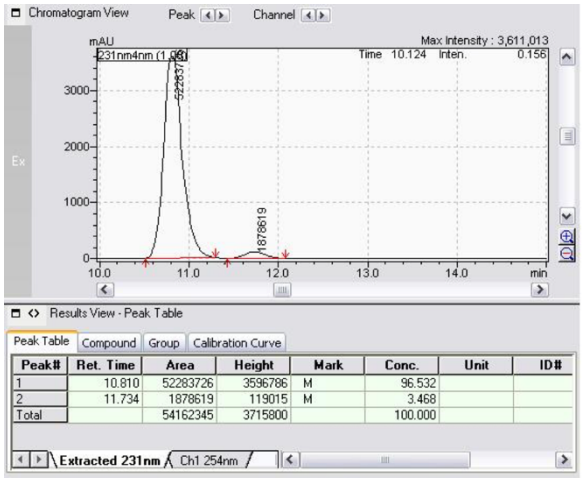




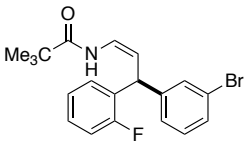
(R,Z)-N-(3-(3-bromophenyl)-3-(4-chlorophenyl)prop-1-en-1-yl)pivalamide **378**

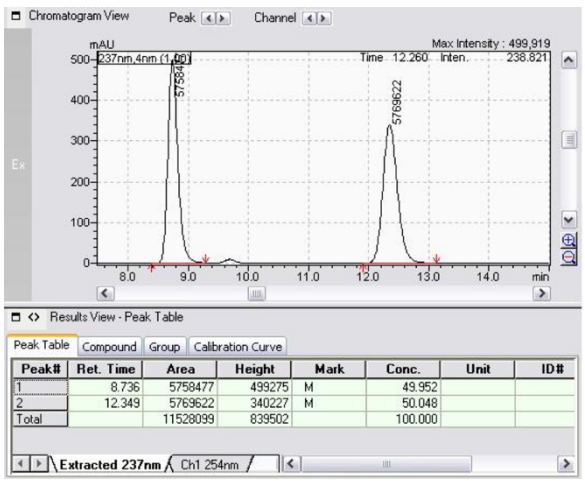


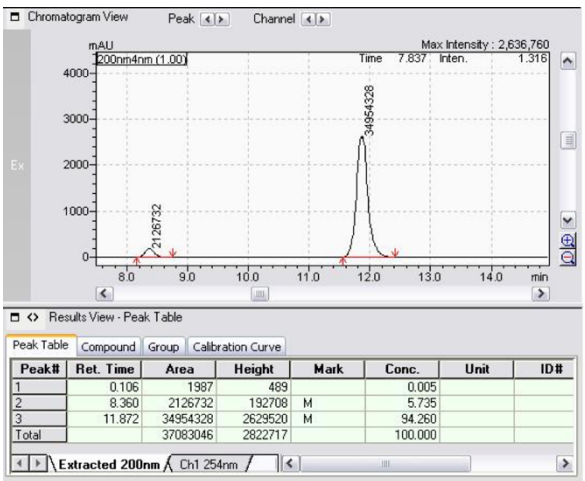




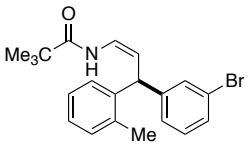
(S,Z)-N-(3-(3-bromophenyl)-3-(2-fluorophenyl)prop-1-en-1-yl)pivalamide **379**

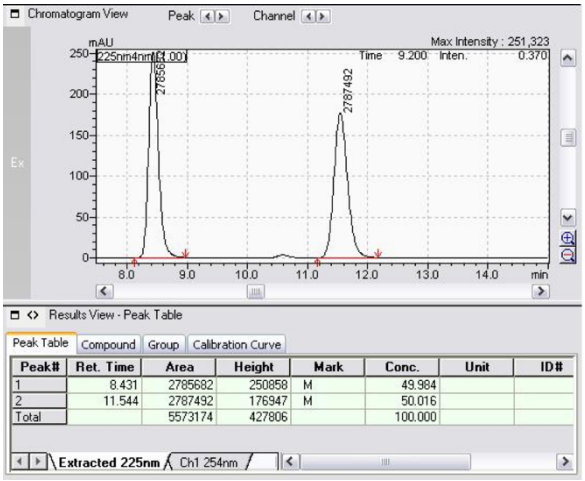


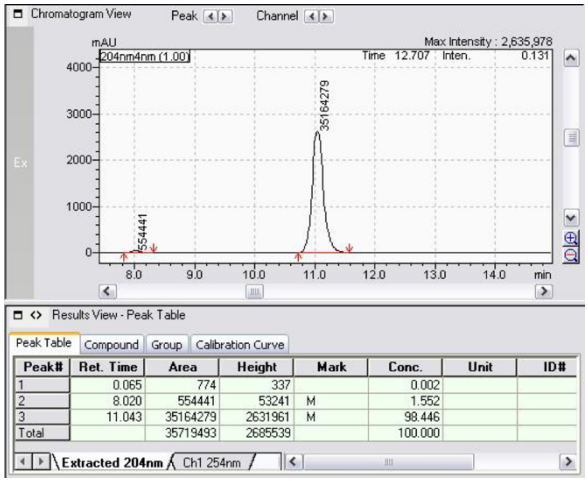




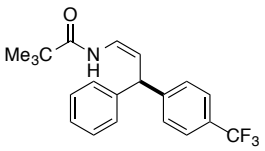
(S,Z)-N-(3-(3-bromophenyl)-3-(o-tolyl)prop-1-en-1-yl)pivalamide **380**

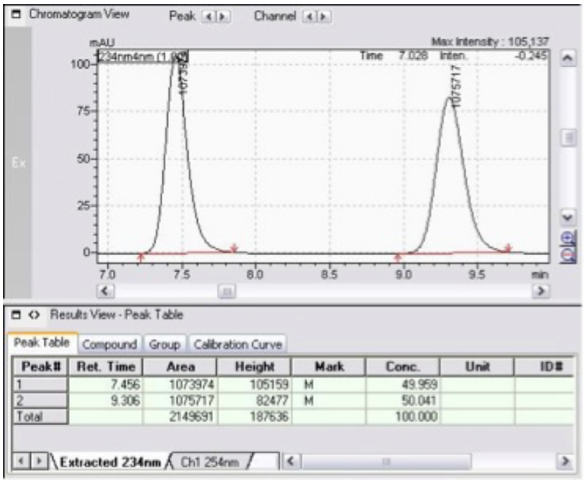


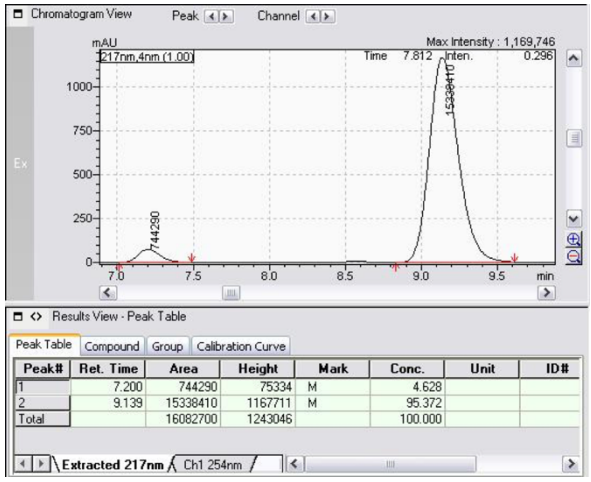




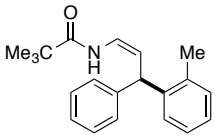
(R)-2,2-dimethyl-N-[(1Z)-3-phenyl-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **383**

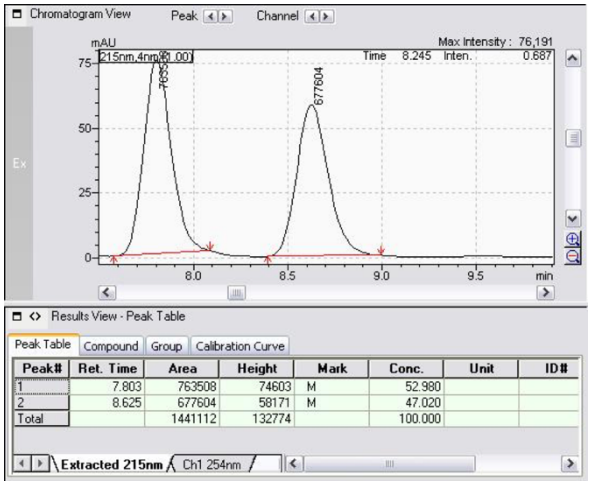


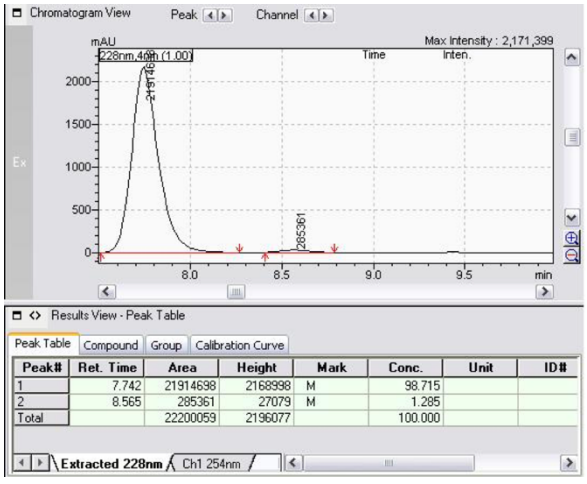




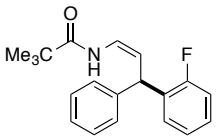
(R)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-phenylprop-1-en-1-yl]propanamide **384**

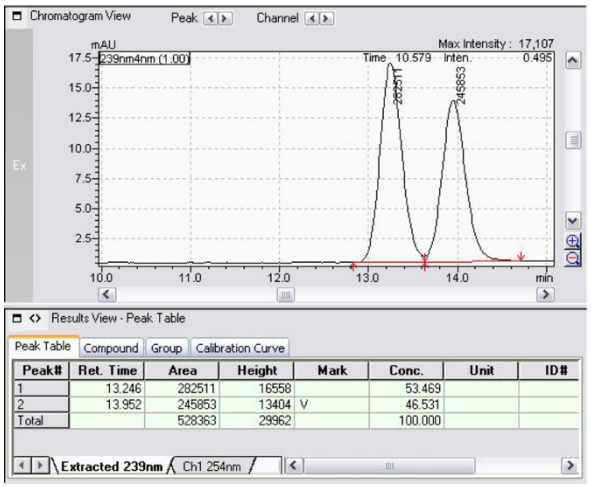


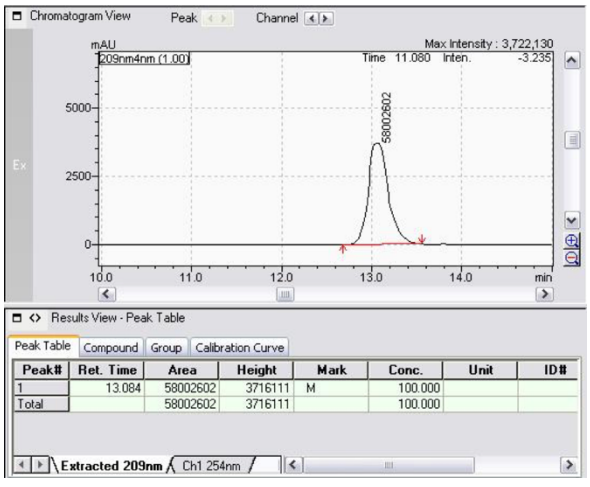




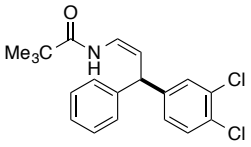
(R)-N-[(1Z)-3-(2-fluorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **385**

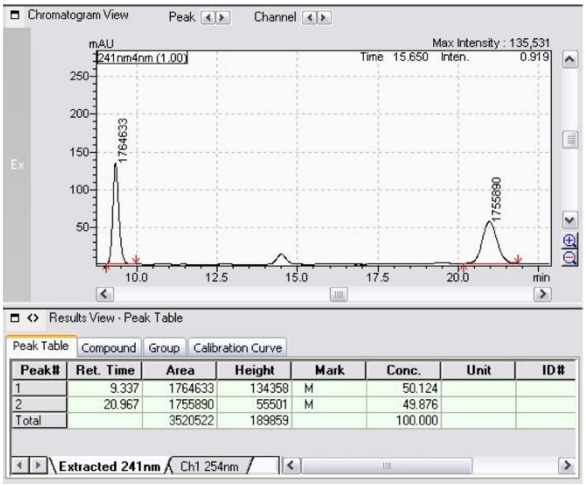


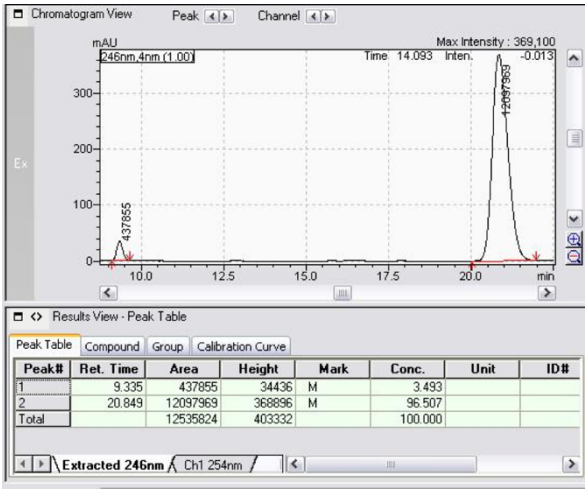




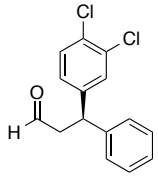
(R)-N-[(1Z)-3-(3,4-dichlorophenyl)-3-phenylprop-1-en-1-yl]-2,2-dimethylpropanamide **389**

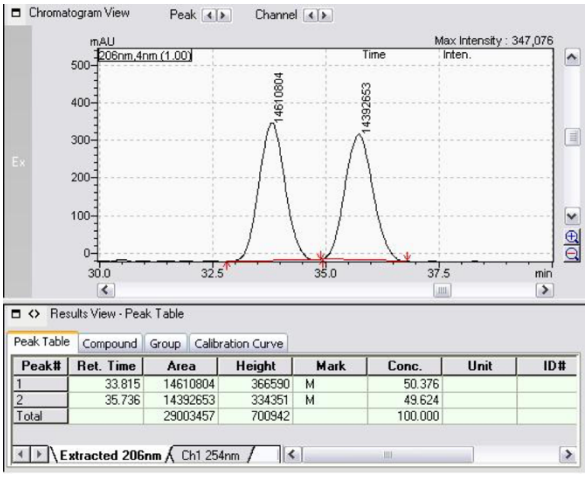


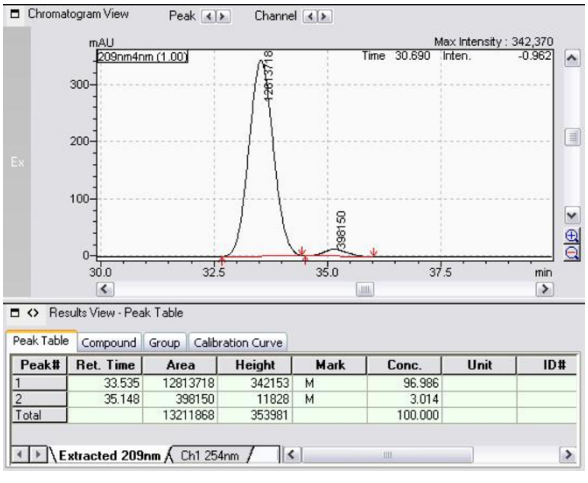




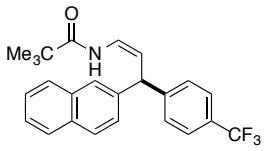
(R)-3-(3,4-dichlorophenyl)-3-phenylpropanal **436** *via reduction to (R)-3-(3,4-dichlorophenyl)-3-phenylpropan-1-ol*

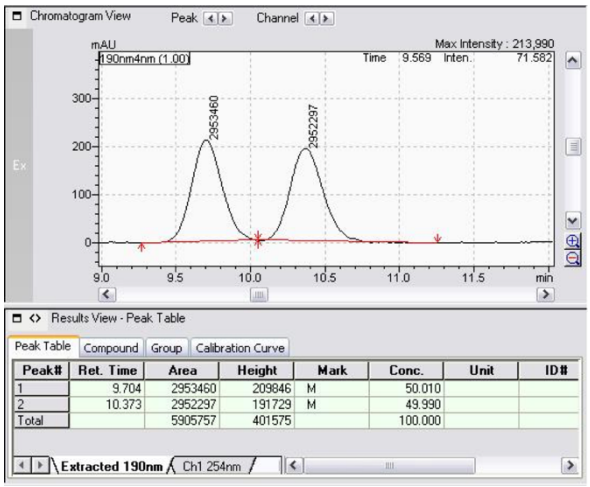


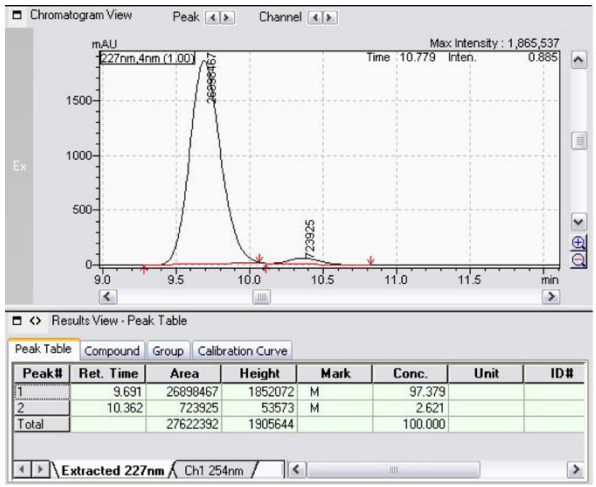




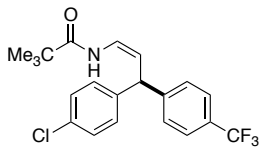
(S)-2,2-dimethyl-N-[(1Z)-3-(naphthalen-2-yl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **396**

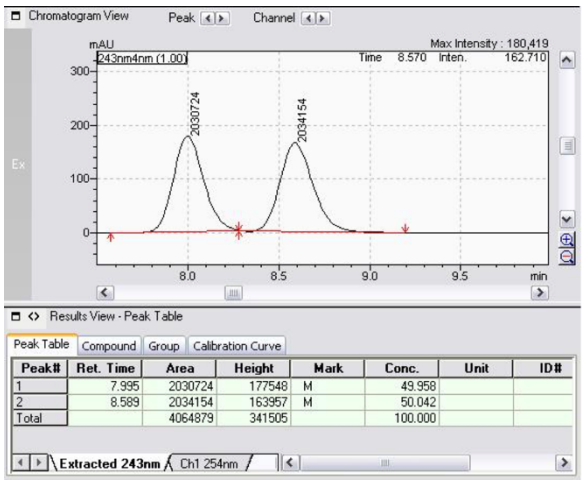


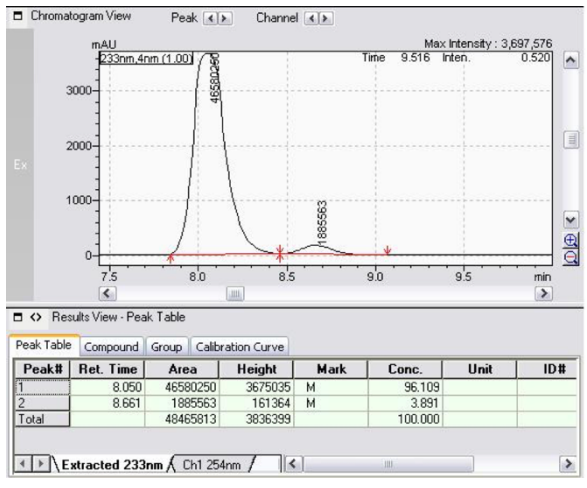




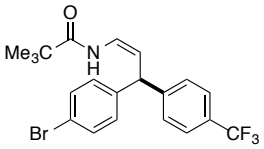
(S)-N-[(1Z)-3-(4-bromophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **398**

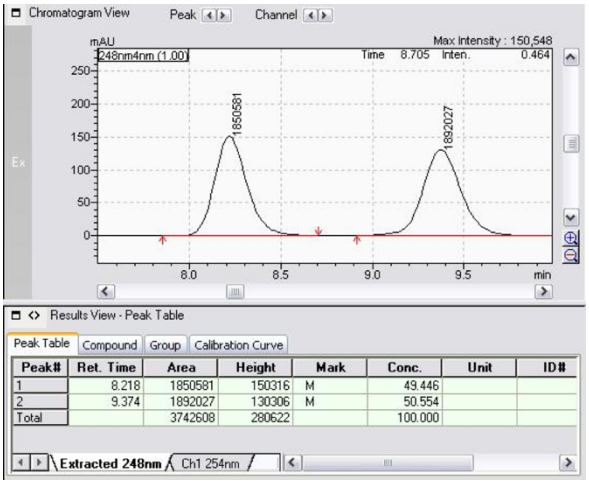


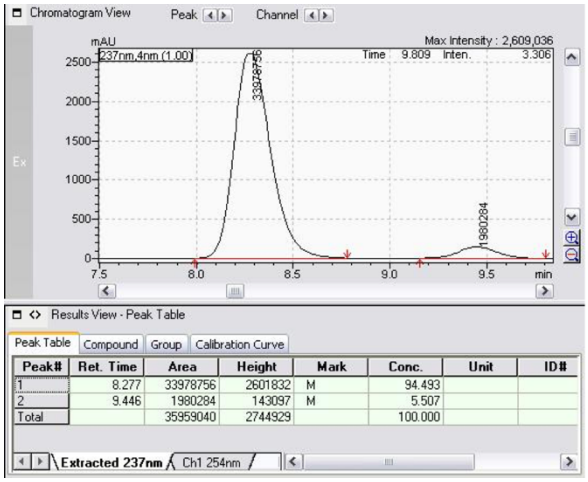




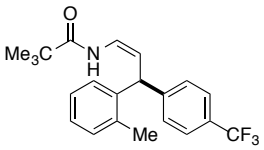
(S)-N-[(1Z)-3-(4-bromophenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-2,2-dimethylpropanamide **399**

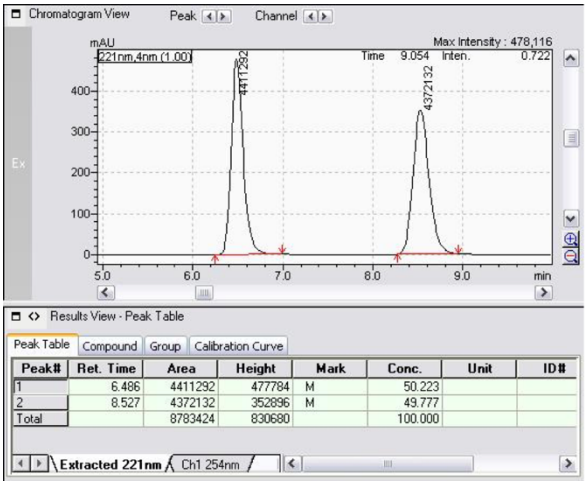


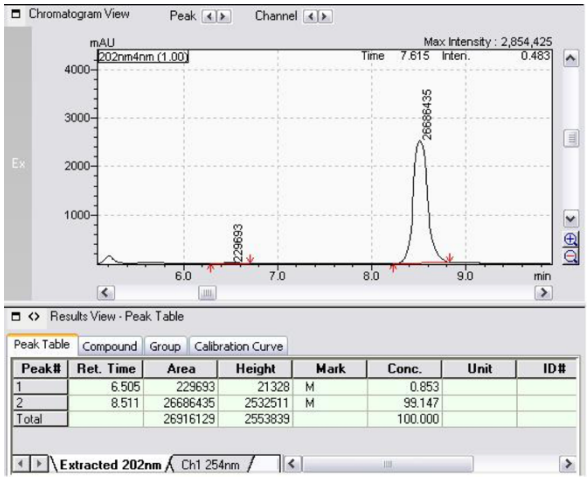




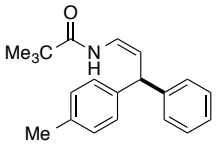
(S)-2,2-dimethyl-N-[(1Z)-3-(2-methylphenyl)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]propanamide **403**

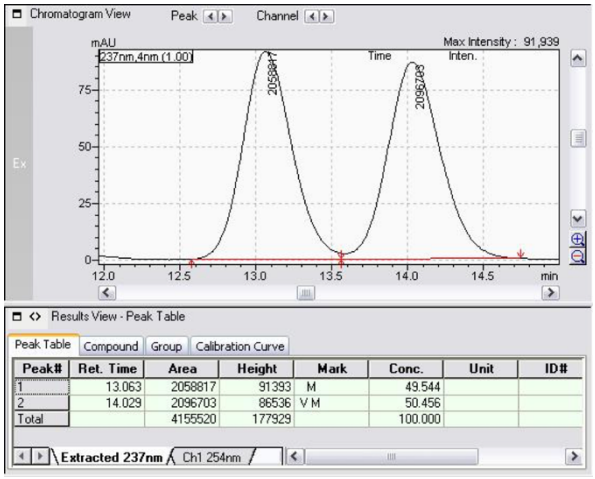


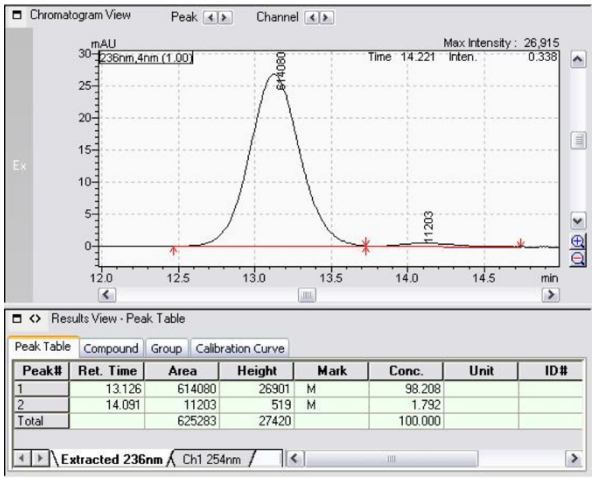




(S,Z)-N-(3-phenyl-3-(p-tolyl)prop-1-en-1-yl)pivalamide **407**

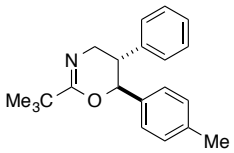


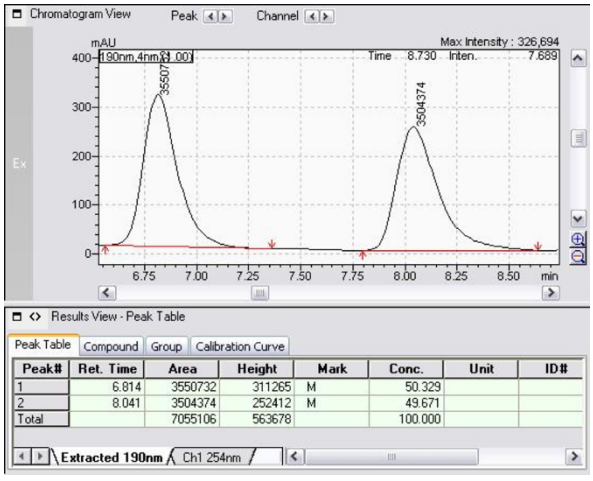


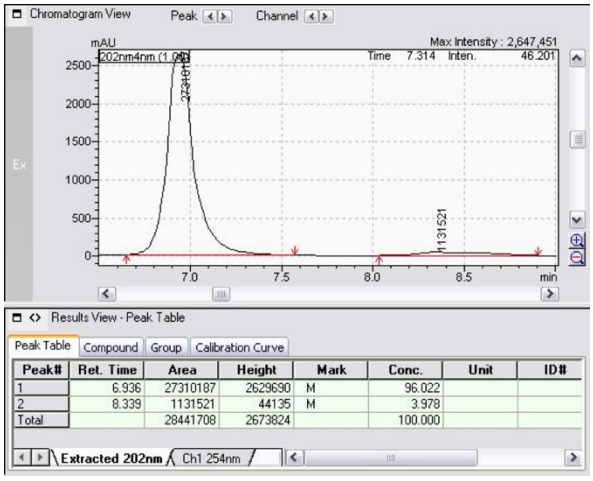


viii.1.2 Oxazine products

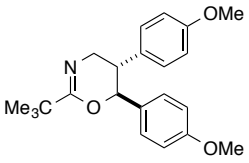
(5R,6R)-2-(tert-butyl)-5-phenyl-6-(4-tolyl)-5,6-dihydro-4H-1,3-oxazine **407**

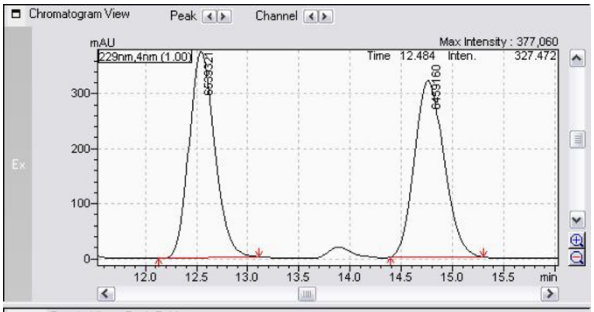


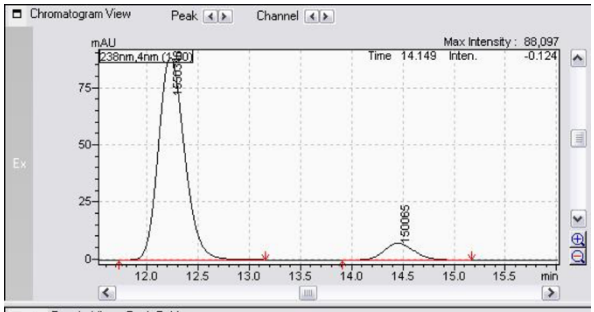




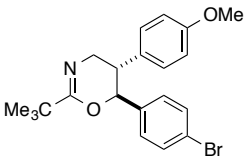
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **410**

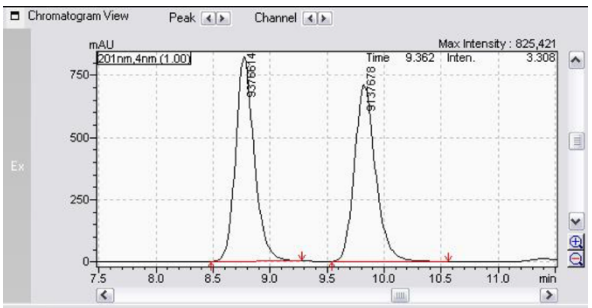


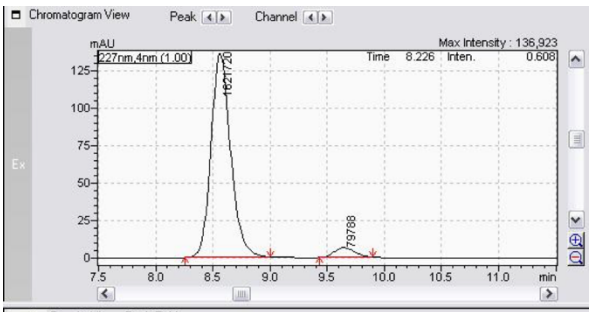




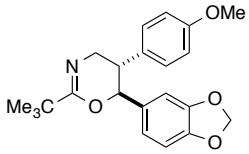
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(4-bromophenyl)-5,6-dihydro-4H-1,3-oxazine **412**

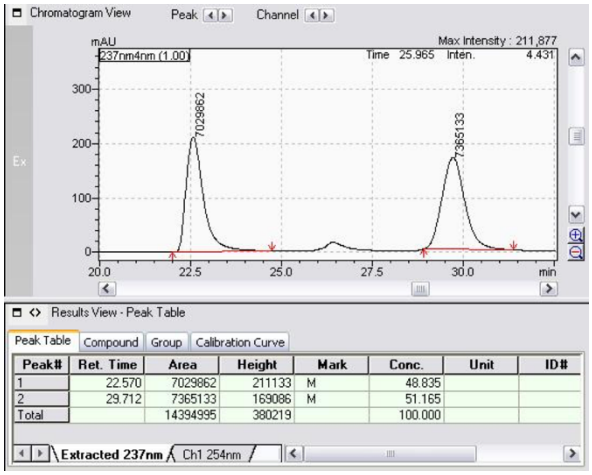


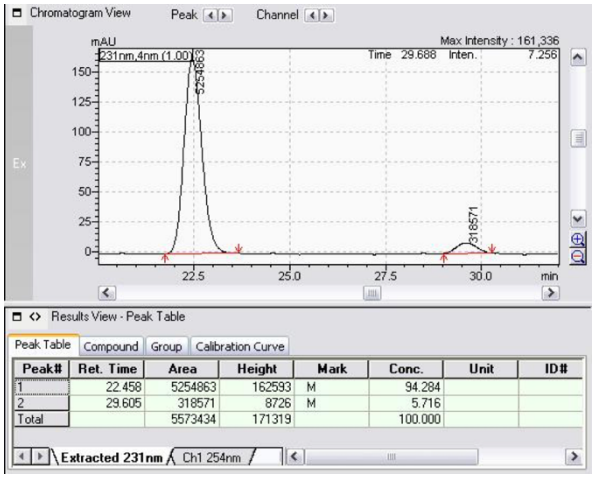




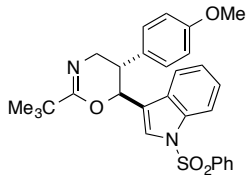
(5S,6S)-6-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butyl)-5-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **414**

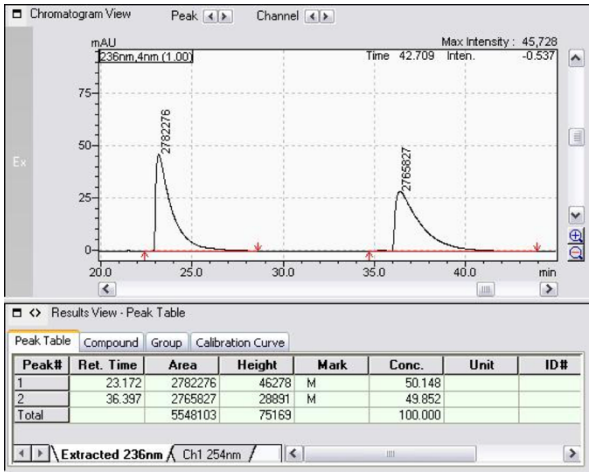


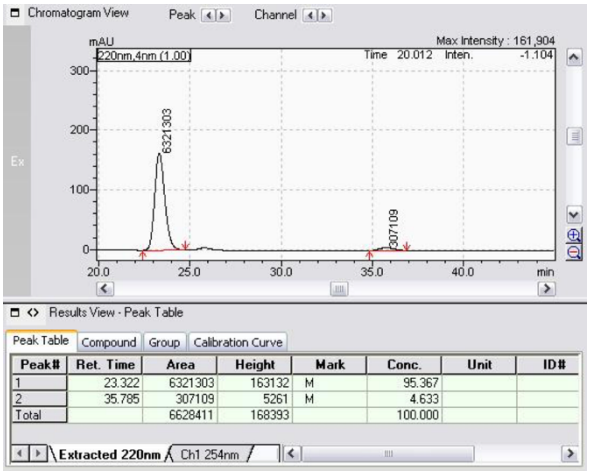




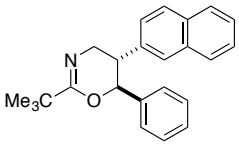
(5S,6S)-2-(tert-butyl)-5-(4-methoxyphenyl)-6-(1-(phenylsulfonyl)-1H-indol-3-yl)-5,6-dihydro-4H-1,3-oxazine **415**

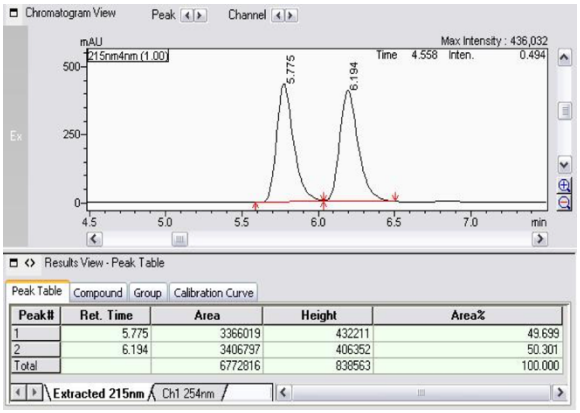


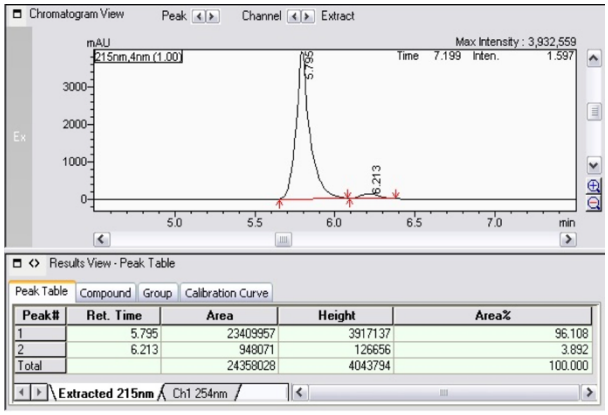




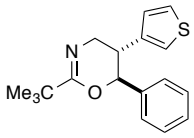
(5S,6S)-2-(tert-butyl)-5-(naphthalen-2-yl)-6-phenyl-5,6-dihydro-4H-1,3-oxazine **423**

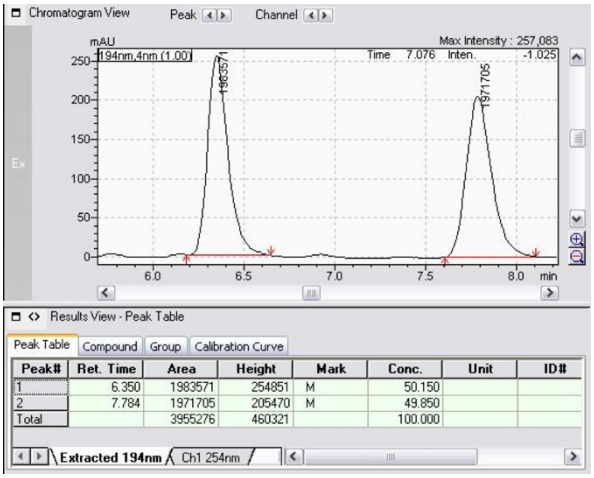


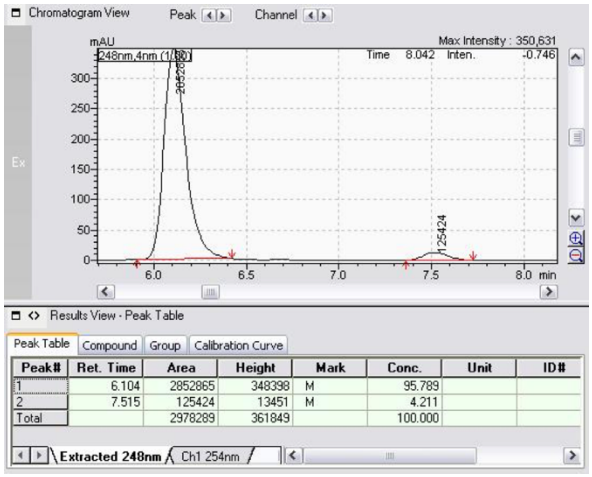




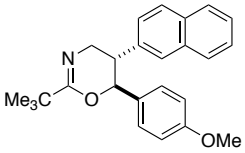
(5S,6S)-2-(tert-butyl)-6-phenyl-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **424**

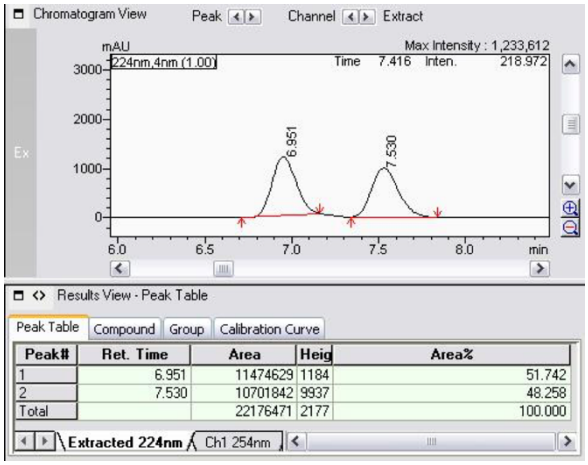


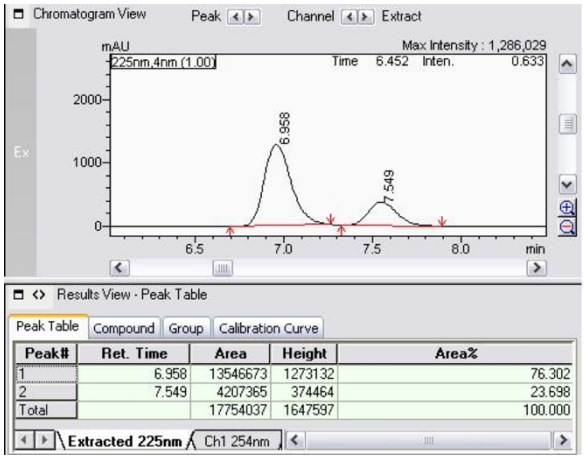




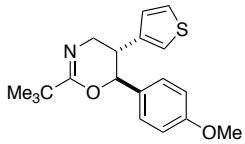
(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(naphthalen-2-yl)-5,6-dihydro-4H-1,3-oxazine **425**

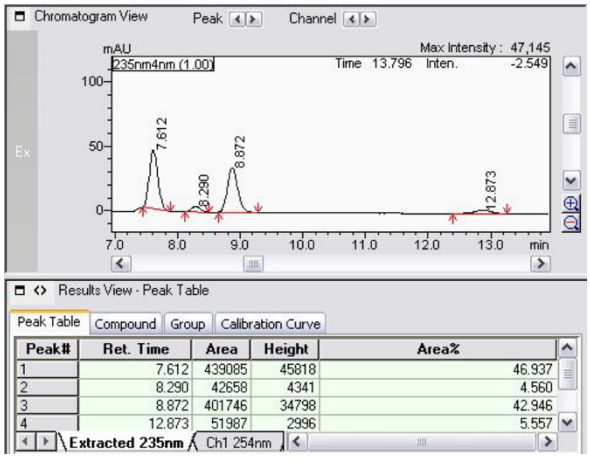


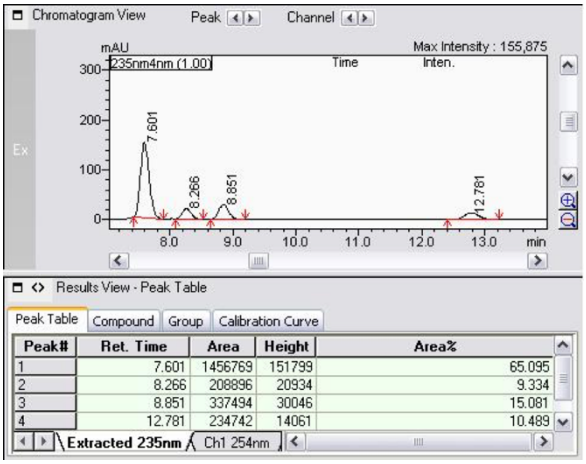




(5S,6S)-2-(tert-butyl)-6-(4-methoxyphenyl)-5-(thiophen-3-yl)-5,6-dihydro-4H-1,3-oxazine **426**

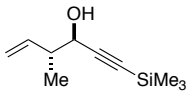




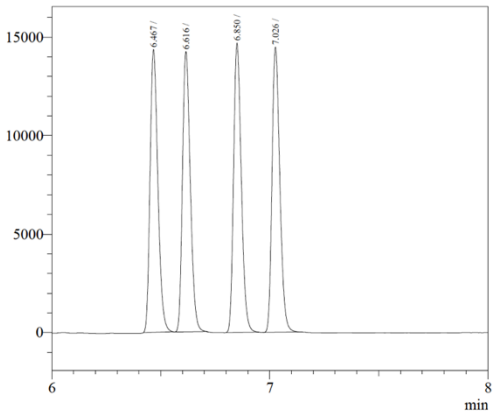


viii.2 Studies Towards the Total Synthesis of (–)-Lyngbyaloside B

(3R,4R)-4-methyl-1-(trimethylsilyl)hex-5-en-1-yn-3-ol **511**

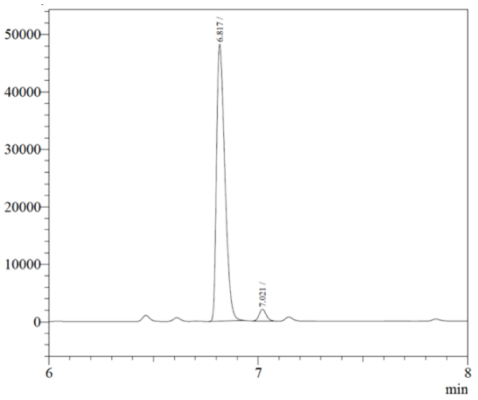


Racemate (Diasteroisomeric mixture):



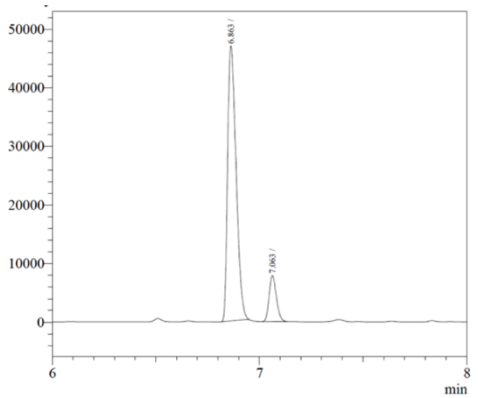
Peak#	Ret.Time	Area
1	6.467	35729
2	6.616	35424
3	6.850	35973
4	7.026	35996
Total		143122

Enantioenriched (Brown Crotylation – Method 1) – 93% e.e.:



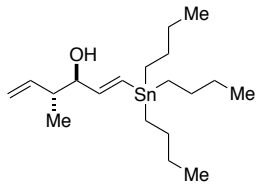
Peak#	Ret.Time	Area
1	6.817	133121
2	7.021	4762
Total		137883

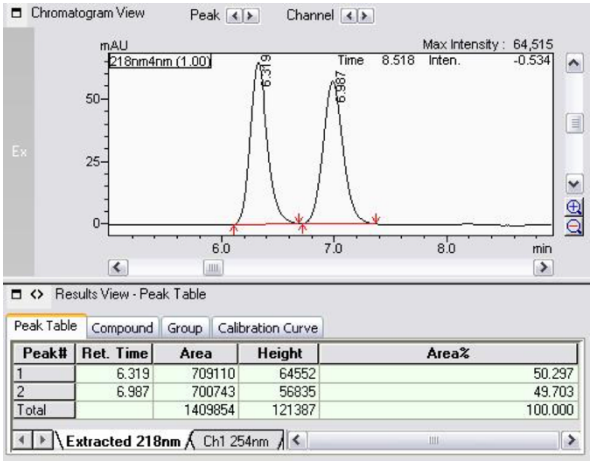
Enantioenriched (Roush Crotylation – Method 2) – 75% e.e.:

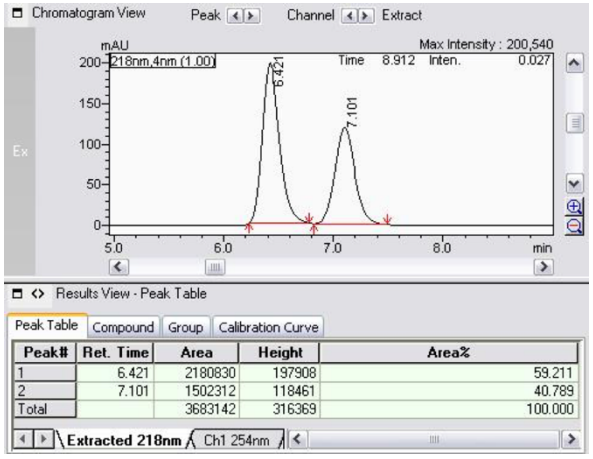


Peak#	Ret.Time	Area
1	6.863	133098
2	7.063	19004
Total		152102

(3R,4R,E)-4-methyl-1-(tributylstannyl)hexa-1,5-dien-3-ol **562**







x Appendix 4 – Computational Experimental

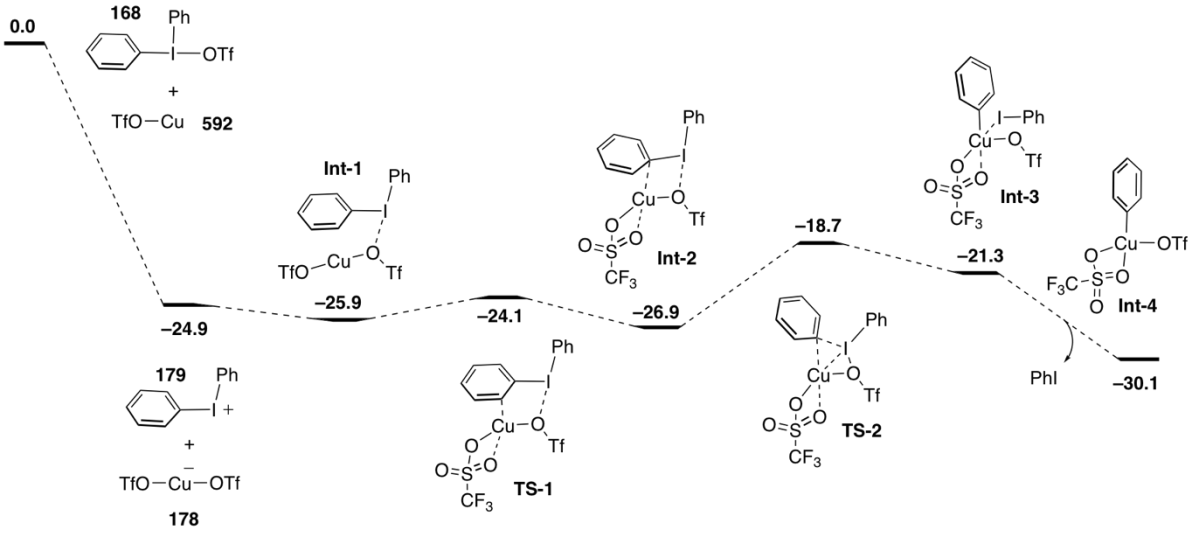
i.1 General Comments

Gaussian 09 version D.01[1] was used for DFT calculations at the BP86[2,3] level. All calculations were carried out with dichloromethane as solvent with the IEFPCM (SCRF) model.[4–7] Calculations employed either the quadruple-ξ valence polarised def2-QZVP basis set on Cu and I with the SDD ECP and the 6-311+G(2d,p) basis set on other atoms *or* the single-ξ valence polarised def2-SVP basis set on Cu and I with the SDD ECP and the 6-31+G(d,p) basis set on other atoms (as stated).[8] All thermodynamic data were calculated at the standard state (298.15 K and 1 atm). All transition structures contained one imaginary frequency. The nature of transition structures was confirmed by vibrational frequency calculations or by intrinsic reaction coordinate (IRC) calculations.

i.2 Calculated Intermediates and Transition States

i.2.1 Oxidative addition of copper(I) triflate into diphenyliodonium triflate

Pathway elaborated as below (Scheme 135).



Scheme 135 – Oxidative addition of copper(I) triflate **592** into diphenyliodonium triflate **168** (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu,I], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

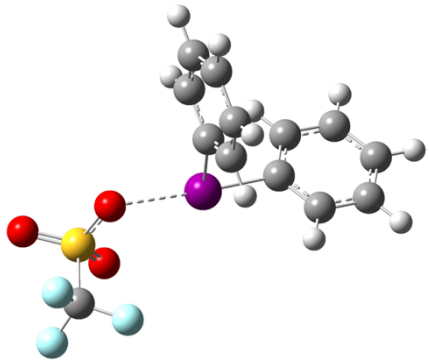
Diphenyliodonium triflate (168):

Energies (Hartree):

Zero-point correction	0.201118
Thermal correction to Energy	0.222647
Thermal correction to Enthalpy	0.223591
Thermal correction to Gibbs Free Energy	0.144109
Sum of electronic and zero-point Energies	-1435.851272
Sum of electronic and thermal Energies	-1435.829742

Sum of electronic and thermal Enthalpies	-1435.828798
Sum of electronic and thermal Free Energies	-1435.908280
E(RB-P86)	-1436.052389

Structure:



Coordinates:

C	-3.902949	-0.491297	0.820392	C	1.036628	1.658914	-0.009944
F	-4.889109	-1.422709	0.765114	C	1.076485	2.192492	1.284977
F	-3.080568	-0.807549	1.856089	C	1.292270	2.413147	-1.162667
F	-4.470766	0.713144	1.084704	C	1.398424	3.555440	1.422319
S	-2.937745	-0.444225	-0.816752	H	0.860803	1.580537	2.164382
O	-2.352307	-1.818836	-0.929472	C	1.609731	3.774281	-0.998169
O	-3.963353	-0.060845	-1.827474	H	1.241543	1.970445	-2.160514
C	2.607728	-1.149201	0.026278	C	1.664576	4.340975	0.287110
C	3.448813	-1.242212	-1.094526	H	1.435110	3.996656	2.423139
C	3.018339	-1.539811	1.311171	H	1.811353	4.385560	-1.883222
C	4.753689	-1.734668	-0.910426	H	1.911869	5.400507	0.404441
C	4.326950	-2.030638	1.473623	O	-1.889021	0.626128	-0.551533
C	5.190468	-2.125825	0.367938	H	3.106125	-0.944830	-2.089679
H	5.424111	-1.813466	-1.771984	H	6.206065	-2.511118	0.501899
H	4.665006	-2.339211	2.467851	H	2.343812	-1.469196	2.169238
I	0.574956	-0.437649	-0.244364				

Copper(I) triflate (592):

Energies (Hartree):

Zero-point correction	0.025739
Thermal correction to Energy	0.035478
Thermal correction to Enthalpy	0.036422
Thermal correction to Gibbs Free Energy	-0.012422
Sum of electronic and zero-point Energies	-1157.145744

Sum of electronic and thermal Energies	-1157.136005
Sum of electronic and thermal Enthalpies	-1157.135061
Sum of electronic and thermal Free Energies	-1157.183905
E(RB-P86)	-1158.156448

Structure:

Coordinates:

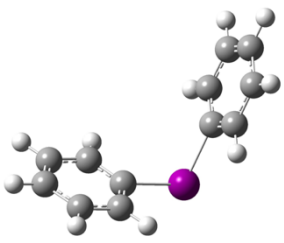
O	0.610714	0.313327	-1.236083	S	-0.187349	0.725456	-0.000033
C	-1.671326	-0.457671	0.000034	O	-0.767830	2.087679	0.000317
F	-2.429000	-0.249358	1.100536	O	0.611231	0.313042	1.235644
F	-2.429376	-0.248854	-1.100112	Cu	2.218468	-0.358904	0.000016
F	-1.246398	-1.742393	-0.000333				

Diphenyliodonium cation (179):

Energies (Hartree):

Zero-point correction	0.175197
Thermal correction to Energy	0.187115
Thermal correction to Enthalpy	0.188059
Thermal correction to Gibbs Free Energy	0.134038
Sum of electronic and zero-point Energies	-474.184977
Sum of electronic and thermal Energies	-474.173059
Sum of electronic and thermal Enthalpies	-474.172115
Sum of electronic and thermal Free Energies	-474.226136
E(RB-P86)	-474.360174

Structure:



Coordinates:

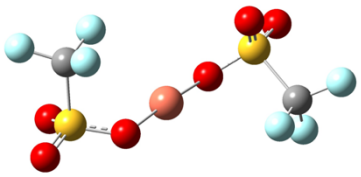
C	-1.665489	0.000701	-0.027141	C	3.401114	1.158584	-1.158191
C	-2.303496	0.278468	1.189904	H	1.970788	-0.164218	-2.131689
C	-2.063480	0.536775	-1.259600	C	3.162651	1.414300	1.258465
C	-3.401226	1.158273	1.158325	H	1.548581	0.286781	2.190504
C	-3.162568	1.414612	-1.258241	C	3.825711	1.722906	0.057295
C	-3.825773	1.722852	-0.057055	H	3.919403	1.396292	-2.092015
H	-3.919601	1.395702	2.092172	H	3.496256	1.850650	2.204777
H	-3.496122	1.851174	-2.204474	H	4.681873	2.404001	0.069757
I	-0.000009	-1.375208	-0.000091	H	-1.970866	-0.164633	2.131614
C	1.665563	0.000602	0.027124	H	-1.548351	0.287456	-2.190444
C	2.303459	0.278694	-1.189904	H	-4.682000	2.403866	-0.069433
C	2.063620	0.536390	1.259690				

Copper(I) triflate anion (178):

Energies (Hartree):

Zero-point correction	0.052707
Thermal correction to Energy	0.071526
Thermal correction to Enthalpy	0.072471
Thermal correction to Gibbs Free Energy	-0.000653
Sum of electronic and zero-point Energies	-2118.852201
Sum of electronic and thermal Energies	-2118.833382
Sum of electronic and thermal Enthalpies	-2118.832438
Sum of electronic and thermal Free Energies	-2118.905561
E(RB-P86)	-2118.904908

Structure:



Coordinates:

O	-1.580651	-1.162686	0.407494	O	1.613696	0.134352	-1.203172
C	-3.247010	0.940207	0.397797	S	2.690314	0.874788	-0.374913
F	-4.446838	1.397684	-0.035370	C	3.534622	-0.568445	0.529676
F	-3.222354	1.006705	1.750458	O	2.137881	1.725736	0.714335

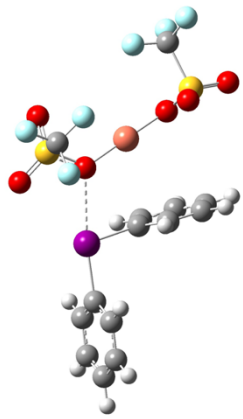
F	-2.275167	1.753533	-0.089360	O	3.742691	1.444021	-1.254710
S	-2.969836	-0.844791	-0.195074	F	4.554340	-0.109833	1.295410
O	-4.032599	-1.642154	0.468434	F	2.645788	-1.206036	1.334322
O	-2.977699	-0.749663	-1.680732	F	4.029935	-1.467140	-0.354974
Cu	-0.001766	-0.451089	-0.384917				

Copper(I) triflate anion – diphenyliodonium cation adduct (Int-1):

Energies (Hartree):

Zero-point correction	0.228549
Thermal correction to Energy	0.261557
Thermal correction to Enthalpy	0.262501
Thermal correction to Gibbs Free Energy	0.152517
Sum of electronic and zero-point Energies	-2593.057248
Sum of electronic and thermal Energies	-2593.024240
Sum of electronic and thermal Enthalpies	-2593.023296
Sum of electronic and thermal Free Energies	-2593.133280
E(RB-P86)	-2593.285797

Structure:



Coordinates:

C	-4.581902	-0.354296	0.117242	O	0.098435	1.171809	-0.465814
C	-5.364768	-0.678035	-1.001822	Cu	1.456153	-0.174989	-0.431298
C	-5.046300	-0.477436	1.436094	S	0.325693	2.679956	-0.808213
C	-6.669083	-1.155645	-0.778949	C	0.904473	3.358721	0.873670
C	-6.353946	-0.956889	1.633321	O	-0.986015	3.329300	-1.062039
C	-7.159675	-1.295095	0.531501	O	1.450527	2.908804	-1.745372
H	-7.297639	-1.415339	-1.636298	F	1.075376	4.697005	0.789652
H	-6.737415	-1.061752	2.652893	F	-0.022080	3.093976	1.824510
I	-2.587896	0.420066	-0.202620	F	2.074656	2.787590	1.235771
C	-1.537923	-1.465589	-0.149775	O	2.752096	-1.569198	-0.490532

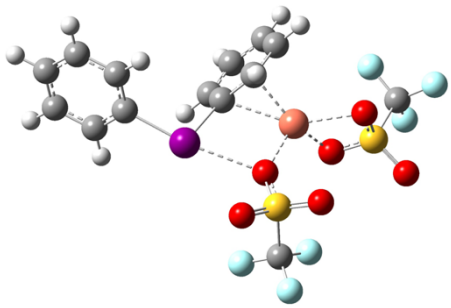
C	-1.039841	-1.911929	1.082786	S	3.857089	-1.687421	0.586774
C	-1.423675	-2.195211	-1.341800	O	4.374313	-3.076426	0.678008
C	-0.395045	-3.162500	1.111810	O	3.546149	-0.959666	1.847925
H	-1.136209	-1.313540	1.992127	C	5.264475	-0.695004	-0.216579
C	-0.773288	-3.441554	-1.282846	F	6.368097	-0.732543	0.569207
H	-1.815418	-1.815681	-2.288829	F	5.579687	-1.210887	-1.428796
C	-0.266964	-3.923139	-0.063053	F	4.897416	0.599291	-0.382784
H	0.011211	-3.530592	2.058689	H	-4.419139	-0.208852	2.290269
H	-0.663531	-4.028772	-2.199582	H	-8.176569	-1.664882	0.694880
H	0.240707	-4.891702	-0.030257	H	-4.982117	-0.563571	-2.019466

Copper(I) triflate anion – diphenyliodonium cation adduct – TS to oxidative addition intermediate (TS-1):

Energies (Hartree):

Zero-point correction	0.227643
Thermal correction to Energy	0.259787
Thermal correction to Enthalpy	0.260731
Thermal correction to Gibbs Free Energy	0.155044
Sum of electronic and zero-point Energies	-2593.057820
Sum of electronic and thermal Energies	-2593.025676
Sum of electronic and thermal Enthalpies	-2593.024732
Sum of electronic and thermal Free Energies	-2593.130419
E(RB-P86)	-2593.285463

Structure:



Coordinates:

C	-4.317769	-0.645290	0.070314	O	0.068286	1.372350	-0.355477
C	-4.854019	-1.285817	-1.058849	Cu	1.080512	-0.478322	-0.355231
C	-4.972085	-0.618899	1.312733	S	0.280766	2.836092	-0.808600
C	-6.088219	-1.945012	-0.921220	C	0.758148	3.672340	0.831477

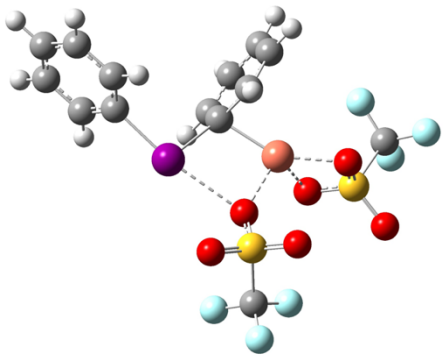
C	-6.207193	-1.283515	1.425340	O	-1.010040	3.471545	-1.195533
C	-6.760777	-1.943659	0.314531	O	1.456836	3.013146	-1.695259
H	-6.523140	-2.453511	-1.787213	F	0.978153	4.993104	0.627151
H	-6.732943	-1.277923	2.385075	F	-0.243820	3.537142	1.736659
I	-2.455736	0.436367	-0.122937	F	1.879291	3.118568	1.344364
C	-1.141573	-1.290397	-0.018542	H	-4.540934	-0.101077	2.173967
C	-1.193206	-2.107166	1.123138	H	-4.335467	-1.276657	-2.021338
C	-0.410726	-1.630103	-1.193940	H	-7.723191	-2.455721	0.409919
C	-0.446765	-3.300499	1.117278	O	3.125284	-0.536114	-1.348400
H	-1.777405	-1.822849	2.001591	S	3.783888	-0.396520	0.010717
C	0.382623	-2.814087	-1.130421	O	2.689630	-0.413166	1.074184
H	-0.572563	-1.116622	-2.148059	O	4.838415	0.634022	0.158776
C	0.345616	-3.642476	0.006496	C	4.695467	-2.041496	0.274019
H	-0.474120	-3.948325	1.998270	F	5.265687	-2.066703	1.502123
H	0.960434	-3.105901	-2.012173	F	3.840283	-3.087397	0.174257
H	0.939663	-4.560348	0.023092	F	5.667069	-2.188955	-0.657896

Oxidative addition intermediate (Int-2):

Energies (Hartree):

Zero-point correction	0.227585
Thermal correction to Energy	0.260600
Thermal correction to Enthalpy	0.261544
Thermal correction to Gibbs Free Energy	0.153295
Sum of electronic and zero-point Energies	-2593.060615
Sum of electronic and thermal Energies	-2593.027600
Sum of electronic and thermal Enthalpies	-2593.026656
Sum of electronic and thermal Free Energies	-2593.134905
E(RB-P86)	-2593.288200

Structure:



Coordinates:

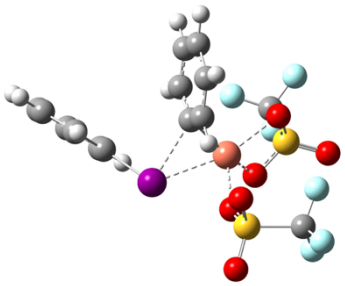
C	-4.170792	-0.474433	0.146519	O	0.247153	1.523785	-0.103528
C	-4.826266	-0.811286	-1.049862	Cu	0.858143	-0.443720	-0.432971
C	-4.718379	-0.741595	1.412724	S	0.436935	2.913426	-0.759349
C	-6.068977	-1.463643	-0.964720	C	1.285768	3.861190	0.652465
C	-5.962111	-1.395463	1.473057	O	-0.872752	3.597578	-0.951001
C	-6.633352	-1.754049	0.290490	O	1.408482	2.916250	-1.880685
H	-6.594682	-1.737409	-1.884637	F	1.518332	5.139953	0.270770
H	-6.404650	-1.616166	2.449281	F	0.493825	3.875747	1.752377
I	-2.309005	0.605328	0.035159	F	2.463292	3.280908	0.972135
C	-0.994217	-1.184957	-0.050476	H	-4.197239	-0.454934	2.330280
C	-0.899593	-1.956918	1.140389	H	-4.389751	-0.577278	-2.024640
C	-0.700717	-1.745481	-1.334206	H	-7.603100	-2.257984	0.347155
C	-0.489181	-3.292088	1.036141	O	2.781561	-0.628957	-1.154482
H	-1.127404	-1.516430	2.114274	S	3.558753	-0.675682	0.168639
C	-0.294358	-3.104182	-1.391481	O	2.577852	-0.643970	1.311931
H	-0.910269	-1.195792	-2.257486	O	4.748824	0.204488	0.240732
C	-0.206286	-3.868625	-0.222187	C	4.272505	-2.435866	0.184622
H	-0.391833	-3.888226	1.948494	F	4.942271	-2.651318	1.342215
H	-0.076583	-3.547243	-2.367798	F	3.283561	-3.356344	0.082080
H	0.089274	-4.919965	-0.281447	F	5.129064	-2.606278	-0.850019

Oxidative addition transition state (TS-2):

Energies (Hartree):

Zero-point correction	0.227389
Thermal correction to Energy	0.259620
Thermal correction to Enthalpy	0.260564
Thermal correction to Gibbs Free Energy	0.155980
Sum of electronic and zero-point Energies	-2593.050441
Sum of electronic and thermal Energies	-2593.018210
Sum of electronic and thermal Enthalpies	-2593.017266
Sum of electronic and thermal Free Energies	-2593.121850
E(RB-P86)	-2593.277830

Structure:



Coordinates:

C	-3.454037	-0.997129	-0.748213	O	1.500781	-1.323266	-0.732228
C	-4.297502	-1.78987	0.048668	Cu	0.393698	0.317978	0.056805
C	-3.924235	0.070664	-1.532168	S	2.515351	-2.410501	-0.347386
C	-5.668325	-1.481096	0.066066	C	4.116356	-1.398018	-0.189045
C	-5.300295	0.357642	-1.498477	O	2.768964	-3.366398	-1.457457
C	-6.166539	-0.412751	-0.702639	O	2.291134	-2.982408	1.012922
H	-6.344315	-2.083188	0.68076	F	5.146617	-2.215281	0.138505
H	-5.688688	1.185331	-2.099581	F	4.40632	-0.782393	-1.358857
I	-1.37364	-1.498664	-0.863834	F	3.989304	-0.456178	0.776823
C	-0.838852	-0.482296	1.396001	H	-3.246947	0.662091	-2.153905
C	-1.773807	0.499015	1.763215	H	-3.907171	-2.619921	0.643265
C	-0.19246	-1.337329	2.30214	H	-7.236172	-0.182695	-0.684135
C	-1.966888	0.717436	3.141353	O	1.292604	2.079915	1.081768
H	-2.32214	1.095196	1.028302	S	1.521937	2.758724	-0.25995
C	-0.410387	-1.090185	3.670859	O	1.016033	1.798928	-1.338046
H	0.496449	-2.122283	1.971622	O	2.834397	3.397642	-0.494567
C	-1.292831	-0.07538	4.085707	C	0.26802	4.18624	-0.294686
H	-2.654751	1.50667	3.460227	F	0.306618	4.805891	-1.495524
H	0.112359	-1.709764	4.406372	F	-0.98612	3.717907	-0.08701
H	-1.468947	0.086486	5.1535	F	0.562683	5.08354	0.672173

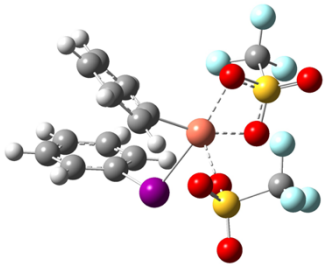
Copper(III)-Ph-IPh-K²OTf-ApicalOTf (Int-3):

Energies (Hartree):

Zero-point correction	0.227238
Thermal correction to Energy	0.260289
Thermal correction to Enthalpy	0.261233
Thermal correction to Gibbs Free Energy	0.153098
Sum of electronic and zero-point Energies	-2593.051908
Sum of electronic and thermal Energies	-2593.018857
Sum of electronic and thermal Enthalpies	-2593.017913

Sum of electronic and thermal Free Energies	-2593.126049
E(RB-P86)	-2593.279147

Structure:



Coordinates:

C	-3.171476	-1.135532	-0.984623	O	1.744581	-1.012524	-0.649940
C	-3.988618	-2.050072	-0.296611	Cu	0.212361	0.255770	0.193493
C	-3.684761	0.002339	-1.632862	S	2.990758	-1.867895	-0.404697
C	-5.370433	-1.798306	-0.249114	C	4.364993	-0.555439	-0.410829
C	-5.069250	0.234198	-1.568659	O	3.308756	-2.760913	-1.550864
C	-5.907915	-0.661486	-0.880267	O	3.043751	-2.464966	0.963032
H	-6.023725	-2.497038	0.282212	F	5.570340	-1.143050	-0.211801
H	-5.487645	1.115690	-2.063899	F	4.392925	0.095136	-1.598139
I	-1.080136	-1.547543	-1.148829	F	4.160548	0.352066	0.574767
C	-0.605243	-0.746036	1.667688	H	-3.030477	0.690231	-2.174733
C	-1.821483	-0.243948	2.127681	H	-3.567517	-2.931301	0.194487
C	0.225976	-1.618530	2.363019	H	-6.985262	-0.474452	-0.838159
C	-2.166944	-0.553722	3.461680	O	0.739365	1.975297	1.281071
H	-2.479340	0.384480	1.519887	S	0.917545	2.821603	0.011264
C	-0.151879	-1.911309	3.694216	O	0.658397	1.867656	-1.151637
H	1.147880	-2.034761	1.938964	O	2.105093	3.692698	-0.055853
C	-1.337669	-1.385322	4.233150	C	-0.573819	4.004506	0.017456
H	-3.093181	-0.141003	3.874500	F	-0.580628	4.725302	-1.123467
H	0.495142	-2.564704	4.288606	F	-1.728026	3.305062	0.103155
H	-1.629697	-1.642822	5.256216	F	-0.486123	4.840236	1.072756

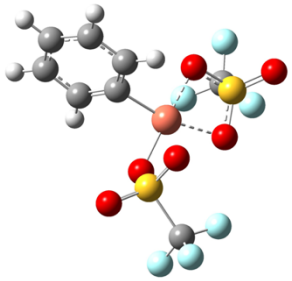
Copper(III)-Ph-K²OTf-OTf (Int-4):

Energies (Hartree):

Zero-point correction	0.139342
Thermal correction to Energy	0.163975
Thermal correction to Enthalpy	0.164919
Thermal correction to Gibbs Free Energy	0.078570
Sum of electronic and zero-point Energies	-2350.184093

Sum of electronic and thermal Energies	-2350.159460
Sum of electronic and thermal Enthalpies	-2350.158516
Sum of electronic and thermal Free Energies	-2350.244864
E(RB-P86)	-2350.323435

Structure:



Coordinates:

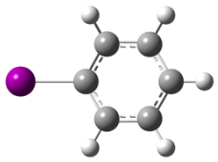
O	-1.235468	-1.619700	-0.179275	F	-4.813364	-0.141593	0.222664
C	0.287403	2.162210	0.042614	F	-4.173855	-2.165787	0.806370
C	0.415346	2.779861	-1.191027	F	-3.267775	-0.405715	1.765386
C	0.362924	2.749939	1.294964	S	-2.434300	-0.873790	-0.746400
C	0.591720	4.185218	-1.145453	O	-3.085591	-1.372274	-1.966260
H	0.370081	2.254404	-2.148043	O	-1.958382	0.613698	-0.790581
C	0.530630	4.156626	1.293604	O	1.458365	-0.142382	0.824152
H	0.308194	2.193271	2.233827	S	2.724423	-0.343118	-0.105708
C	0.645747	4.859681	0.084228	O	3.903938	0.350269	0.452479
H	0.680594	4.726037	-2.093441	O	2.370987	-0.194751	-1.538943
H	0.584152	4.674075	2.257070	F	3.234568	-2.440389	1.498463
H	0.792663	5.944141	0.100277	C	3.035331	-2.201678	0.185626
Cu	-0.187773	0.263886	-0.004212	F	4.135307	-2.571971	-0.504590
C	-3.770925	-0.895856	0.616362	F	1.979327	-2.922210	-0.242949

Iodobenzene:

Energies (Hartree):

Zero-point correction	0.087425
Thermal correction to Energy	0.093474
Thermal correction to Enthalpy	0.094418
Thermal correction to Gibbs Free Energy	0.055527
Sum of electronic and zero-point Energies	-242.863274
Sum of electronic and thermal Energies	-242.857224
Sum of electronic and thermal Enthalpies	-242.856280
Sum of electronic and thermal Free Energies	-242.895172
E(RB-P86)	-242.950698

Structure:

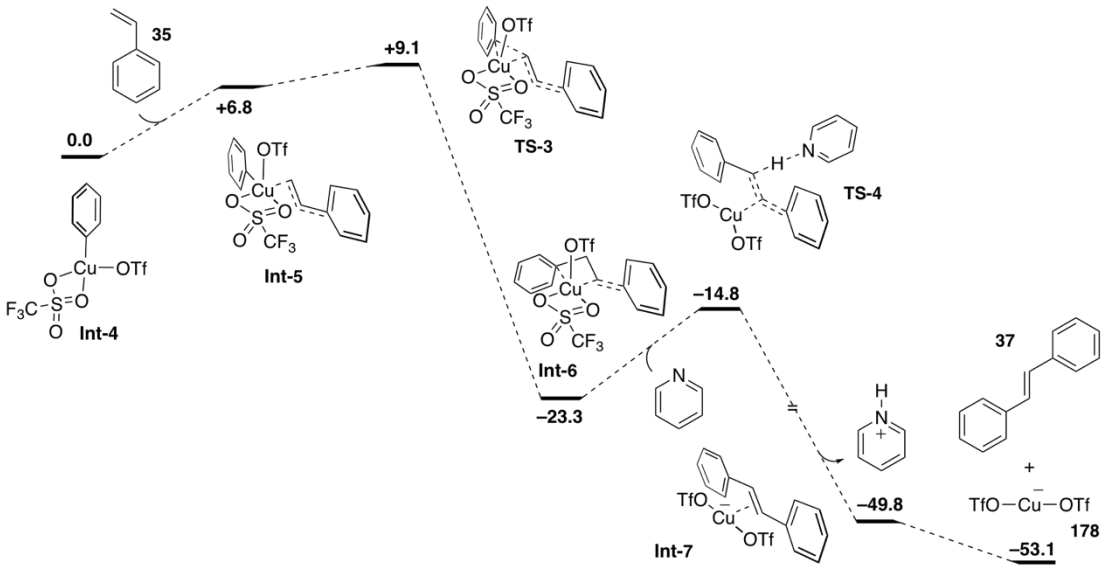


Coordinates:

I	-1.570945	0.000000	-0.000144	C	2.670832	-1.216353	0.000305
C	0.578320	-0.000039	0.000057	H	0.718087	-2.174079	0.000180
C	1.263070	1.226055	0.000052	C	3.375829	0.000024	0.000304
C	1.263109	-1.226080	0.000181	H	3.211008	2.168848	0.000184
C	2.670768	1.216391	0.000185	H	3.211070	-2.168812	0.000401
H	0.717957	2.174001	-0.000043	H	4.470393	0.000071	0.000401

i.2.2 Styrene functionalisation towards stilbene

Pathway elaborated as below (Scheme 138).



Scheme 138 – Association of styrene **35** to key κ²-bound copper(III) species **Int-4** and reaction towards *trans*-stilbene production (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S,N]); energies given as ΔG (kcal mol^{-1})

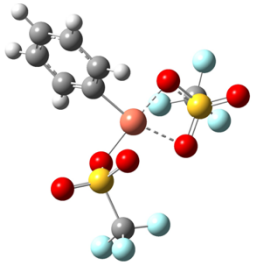
Copper(III)-Ph-K²OTf-OTf (Int-5):

Energies (Hartree):

Zero-point correction	0.139508
Thermal correction to Energy	0.163932
Thermal correction to Enthalpy	0.164876

Thermal correction to Gibbs Free Energy	0.079374
Sum of electronic and zero-point Energies	-2351.442866
Sum of electronic and thermal Energies	-2351.418443
Sum of electronic and thermal Enthalpies	-2351.417499
Sum of electronic and thermal Free Energies	-2351.503000
E(RB-P86)	-2351.582374

Structure:



Coordinates:

O	-1.120879	-1.698428	-0.265292	F	-4.674137	-0.315938	0.297984
C	0.128937	2.169158	0.034240	F	-3.939456	-2.294547	0.891730
C	0.339372	2.800317	-1.172389	F	-3.026324	-0.487570	1.735178
C	0.038557	2.752236	1.279420	S	-2.337927	-0.998759	-0.786523
C	0.419253	4.207616	-1.112434	O	-3.027853	-1.515992	-1.952440
H	0.428552	2.279225	-2.126049	O	-1.926806	0.487875	-0.871439
C	0.115444	4.160325	1.296232	O	1.443737	-0.049899	0.809215
H	-0.083601	2.190745	2.206327	S	2.697762	-0.239496	-0.109954
C	0.306838	4.873103	0.110291	O	3.840367	0.492027	0.422606
H	0.571235	4.757217	-2.044297	O	2.341175	-0.139971	-1.526696
H	0.036488	4.672788	2.257764	F	3.266223	-2.268245	1.542303
H	0.379528	5.962394	0.140637	C	3.073196	-2.070429	0.226709
Cu	-0.184734	0.265292	-0.045519	F	4.191499	-2.409458	-0.440629
C	-3.588713	-1.024993	0.639225	F	2.056918	-2.841204	-0.193910

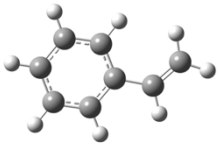
Styrene (35):

Energies (Hartree):

Zero-point correction	0.128916
Thermal correction to Energy	0.135878
Thermal correction to Enthalpy	0.136822
Thermal correction to Gibbs Free Energy	0.097514
Sum of electronic and zero-point Energies	-309.598053
Sum of electronic and thermal Energies	-309.591091
Sum of electronic and thermal Enthalpies	-309.590147

Sum of electronic and thermal Free Energies	-309.629455
E(RB-P86)	-309.726969

Structure:



Coordinates:

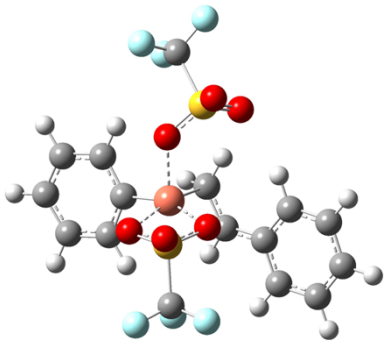
C	-2.270205	0.263992	-0.000003	H	-0.034149	-2.314717	-0.000005
C	-1.786044	-1.048656	-0.000005	H	0.700105	1.943998	0.000011
C	-0.407950	-1.286508	-0.000005	H	-1.733282	2.362686	-0.000004
C	0.517805	-0.222176	0.000010	C	1.957332	-0.533089	0.000009
C	0.011464	1.095703	0.000007	C	2.982662	0.337287	-0.000014
C	-1.363179	1.334380	0.000004	H	2.190701	-1.604798	0.000043
H	-3.345909	0.454935	-0.000007	H	4.014856	-0.017927	-0.000008
H	-2.482600	-1.890653	-0.000014	H	2.838967	1.420879	-0.000036

Copper(III)-styrene-Ph-K²OTf-apicalOTf – towards stilbene (Int-5):

Energies (Hartree):

Zero-point correction	0.270786
Thermal correction to Energy	0.303617
Thermal correction to Enthalpy	0.304561
Thermal correction to Gibbs Free Energy	0.200194
Sum of electronic and zero-point Energies	-2661.051018
Sum of electronic and thermal Energies	-2661.018187
Sum of electronic and thermal Enthalpies	-2661.017243
Sum of electronic and thermal Free Energies	-2661.121610
E(RB-P86)	-2661.321803

Structure:



Coordinates:

C	0.725433	2.224536	-1.040272	H	-0.212214	-2.676355	-1.315497
C	-0.197230	3.165312	-1.476413	C	-3.452657	-3.685596	-1.659088
C	2.087862	2.452902	-0.918433	H	-5.109929	-2.455652	-2.324484
C	0.281319	4.467669	-1.706767	H	-1.635447	-4.680777	-1.021831
H	-1.258926	2.947874	-1.599380	O	-1.285822	-0.668901	0.894429
C	2.537302	3.764064	-1.157450	S	-1.527985	0.398390	1.928884
H	2.783055	1.667503	-0.622463	O	-0.684862	1.583887	1.525325
C	1.639229	4.760842	-1.550275	O	-1.503749	0.004565	3.330079
H	-0.427216	5.241504	-2.011256	C	-3.306767	0.966370	1.611336
H	3.600990	3.983834	-1.039602	F	-4.156584	-0.054983	1.826080
H	2.002517	5.771284	-1.749809	F	-3.617574	1.979948	2.440125
Cu	0.029736	0.612898	-0.243867	F	-3.444679	1.387855	0.336467
C	0.315133	-0.091567	-2.151594	H	-4.071784	-4.575246	-1.523572
C	-1.082457	-0.234356	-2.264228	H	0.951326	-0.939972	-1.868856
H	0.782081	0.672921	-2.774918	O	1.784252	-0.230305	0.762857
C	-1.857539	-1.408900	-2.007156	S	2.367430	-1.614288	0.675529
H	-1.638689	0.621666	-2.663588	O	2.016307	-2.334239	-0.568120
C	-3.253091	-1.361772	-2.280227	O	2.295426	-2.380980	1.924663
C	-1.278713	-2.625702	-1.546066	C	4.207504	-1.230321	0.469681
C	-4.040515	-2.492576	-2.110331	F	4.916516	-2.373687	0.340867
H	-3.695508	-0.427061	-2.632968	F	4.417557	-0.476083	-0.638235
C	-2.076310	-3.747851	-1.377162	F	4.681746	-0.552130	1.537207

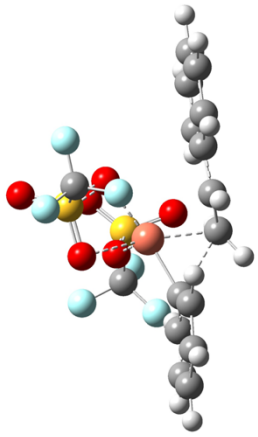
Copper(III)-styrene-Ph-K²OTf-apicalOTf – TS – towards stilbene (TS-3):

Energies (Hartree):

Zero-point correction	0.270736
Thermal correction to Energy	0.302747
Thermal correction to Enthalpy	0.303691
Thermal correction to Gibbs Free Energy	0.202851

Sum of electronic and zero-point Energies	-2661.050188
Sum of electronic and thermal Energies	-2661.018178
Sum of electronic and thermal Enthalpies	-2661.017234
Sum of electronic and thermal Free Energies	-2661.118073
E(RB-P86)	-2661.320924

Structure:



Coordinates:

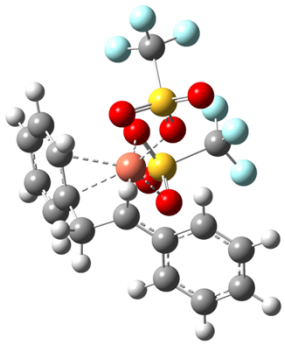
C	0.649991	2.026403	-1.335466	H	0.241651	-2.684758	-1.425903
C	-0.299992	2.960416	-1.742521	C	-2.835095	-4.159124	-1.449629
C	2.003998	2.308366	-1.187812	H	-4.717213	-3.180652	-1.89945
C	0.123133	4.291558	-1.880339	H	-0.83305	-4.87905	-1.035579
H	-1.346611	2.703695	-1.912666	O	-1.393799	-0.57295	0.875637
C	2.400013	3.646414	-1.339533	S	-1.658325	0.533705	1.873937
H	2.72616	1.53911	-0.917981	O	-0.836355	1.712964	1.458479
C	1.466032	4.629529	-1.683522	O	-1.663918	0.155313	3.281913
H	-0.610129	5.053703	-2.153008	C	-3.442133	1.044222	1.503061
H	3.450897	3.904575	-1.190562	F	-4.283033	0.029175	1.780852
H	1.790061	5.664087	-1.81433	F	-3.781394	2.111047	2.252447
Cu	-0.059822	0.530463	-0.325107	F	-3.574405	1.371416	0.198889
C	0.286514	-0.023465	-2.305468	H	-3.298618	-5.131945	-1.271143
C	-1.083969	-0.386916	-2.222014	H	1.075737	-0.749528	-2.073276
H	0.53974	0.705223	-3.077095	O	1.678552	-0.131594	0.772385
C	-1.63674	-1.668644	-1.908873	S	2.393174	-1.452091	0.655358
H	-1.808412	0.367511	-2.550475	O	2.325529	-2.043074	-0.699115
C	-3.046265	-1.82601	-2.0274	O	2.179509	-2.361974	1.786267
C	-0.839207	-2.789594	-1.543277	C	4.198137	-0.913699	0.822905
C	-3.636653	-3.06222	-1.803863	F	5.013726	-1.988872	0.756478
H	-3.656591	-0.963352	-2.3042	F	4.540443	-0.062503	-0.176733
C	-1.441975	-4.018691	-1.318248	F	4.408304	-0.289002	2.000564

Copper-OTf$_2$-stilbenium adduct (Int-6):

Energies (Hartree):

Zero-point correction	0.273378
Thermal correction to Energy	0.305598
Thermal correction to Enthalpy	0.306543
Thermal correction to Gibbs Free Energy	0.203930
Sum of electronic and zero-point Energies	-2661.100062
Sum of electronic and thermal Energies	-2661.067841
Sum of electronic and thermal Enthalpies	-2661.066897
Sum of electronic and thermal Free Energies	-2661.169509
E(RB-P86)	-2661.373439

Structure:



Coordinates:

O	-1.139408	0.800617	-0.749370	O	2.411074	-3.041299	-0.256889
C	0.451468	0.011096	2.868063	O	2.008197	-0.546703	-0.326835
C	1.366615	-1.039999	3.121640	F	0.786903	-3.201312	-2.832634
C	-0.933436	-0.295503	2.718611	C	1.348228	-2.027222	-2.476012
C	0.907333	-2.343905	3.271761	F	2.571038	-1.943067	-3.042910
H	2.429552	-0.814037	3.228007	F	0.585855	-1.021306	-2.941586
C	-1.375865	-1.622503	2.863001	C	0.911539	1.476039	2.866618
H	-1.662436	0.509677	2.591757	C	0.629954	1.990888	1.481844
C	-0.462579	-2.636532	3.143496	C	1.615331	2.415266	0.540422
H	1.616825	-3.144112	3.490552	H	-0.393943	2.343953	1.305067
H	-2.439199	-1.847097	2.766971	C	1.180254	3.100680	-0.635558
H	-0.809722	-3.664849	3.261922	C	3.014330	2.232568	0.748746
Cu	0.100706	0.051040	0.680541	C	2.103648	3.611891	-1.534138
C	-3.669785	-0.049719	-0.838843	H	0.110874	3.222081	-0.814194
F	-4.953821	0.348504	-0.704063	C	3.927580	2.741544	-0.161188
F	-3.500643	-0.547345	-2.080341	H	3.373143	1.696846	1.627594
F	-3.431223	-1.033595	0.055432	C	3.477387	3.432458	-1.300308
S	-2.511458	1.417050	-0.545525	H	1.764626	4.146301	-2.423032
O	-2.850860	2.366228	-1.609843	H	4.997384	2.604731	0.005122

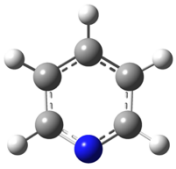
O	-2.766610	1.826463	0.847341	H	4.204044	3.829501	-2.012592
O	0.101927	-2.030200	-0.084122	H	1.974056	1.532782	3.129403
S	1.510474	-1.939059	-0.593007	H	0.340508	2.056158	3.608003

Pyridine:

Energies (Hartree):

Zero-point correction	0.085831
Thermal correction to Energy	0.090249
Thermal correction to Enthalpy	0.091193
Thermal correction to Gibbs Free Energy	0.058348
Sum of electronic and zero-point Energies	-248.270502
Sum of electronic and thermal Energies	-248.266084
Sum of electronic and thermal Enthalpies	-248.265139
Sum of electronic and thermal Free Energies	-248.297985
E(RB-P86)	-248.356332

Structure:



Coordinates:

C	1.201554	0.674943	0.000000	H	-0.000283	2.481559	0.000001
C	-0.000192	1.389116	-0.000017	H	-2.165819	1.187449	0.000037
C	-1.201720	0.674672	0.000008	H	-2.072774	-1.310927	0.000037
C	-1.148797	-0.723058	-0.000003	H	2.073089	-1.310440	0.000026
C	1.149007	-0.722746	0.000018	N	0.000169	-1.427605	-0.000021
H	2.165487	1.188035	0.000005				

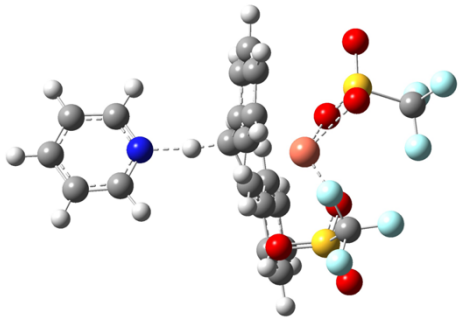
Copper-OTf$_2$-stilbenium adduct – TS – elimination with pyridine (TS-4):

Energies (Hartree):

Zero-point correction	0.356687
Thermal correction to Energy	0.394838
Thermal correction to Enthalpy	0.395782
Thermal correction to Gibbs Free Energy	0.275201
Sum of electronic and zero-point Energies	-2909.372429
Sum of electronic and thermal Energies	-2909.334277
Sum of electronic and thermal Enthalpies	-2909.333333

Sum of electronic and thermal Free Energies	-2909.453914
E(RB-P86)	-2909.729116

Structure:



Coordinates:

O	1.654614	1.261802	0.641712	C	-1.860623	-0.749190	-0.110442
C	-1.365947	-0.387815	-1.509837	C	-1.286265	0.014714	0.977449
C	-1.313540	-1.393094	-2.500617	C	-1.090305	-0.455491	2.319884
C	-1.009681	0.937471	-1.865979	H	-1.245903	1.107093	0.868041
C	-0.920074	-1.088638	-3.802345	C	-0.865191	0.507752	3.342031
H	-1.579094	-2.419460	-2.236094	C	-1.131798	-1.831901	2.671256
C	-0.601923	1.227290	-3.181032	C	-0.719167	0.112903	4.666226
H	-1.115695	1.761989	-1.156229	H	-0.819839	1.565182	3.071643
C	-0.558337	0.222864	-4.146582	C	-0.982002	-2.217881	3.996939
H	-0.887093	-1.880505	-4.553880	H	-1.264006	-2.590488	1.899019
H	-0.332622	2.252504	-3.441558	C	-0.777692	-1.249800	4.995089
H	-0.242602	0.454741	-5.165858	H	-0.553352	0.858674	5.445659
Cu	0.555372	-0.086575	-0.324096	H	-1.011544	-3.276083	4.263221
C	2.297047	3.586949	-0.508281	H	-0.654508	-1.562883	6.034332
F	2.153360	4.926352	-0.397382	H	-1.830385	-1.836129	0.048149
F	3.611426	3.289696	-0.459037	H	-3.057765	-0.503336	-0.100960
F	1.814494	3.204886	-1.710750	N	-4.643355	-0.293143	-0.256185
S	1.367695	2.729360	0.899846	C	-5.188845	0.857688	0.173205
O	2.031954	3.214577	2.112491	C	-5.428799	-1.244749	-0.790409
O	-0.045005	3.099912	0.695912	C	-6.559651	1.104067	0.081463
O	2.226436	-1.039141	-1.616457	H	-4.502442	1.595122	0.598094
S	2.049439	-2.341185	-0.909297	C	-6.808395	-1.075990	-0.917843
O	1.952566	-3.549373	-1.731217	H	-4.931439	-2.159852	-1.121300
O	0.999631	-2.181035	0.158598	C	-7.381933	0.119323	-0.474097
F	4.703676	-2.633775	-0.768834	H	-6.967825	2.050274	0.439695
C	3.648907	-2.574562	0.072361	H	-7.415135	-1.869253	-1.357004

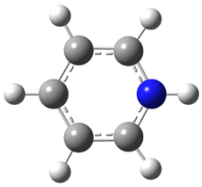
F	3.595245	-3.727672	0.775164	H	-8.458188	0.281840	-0.560298
F	3.839213	-1.555372	0.933025				

Pyridium ion:

Energies (Hartree):

Zero-point correction	0.100056
Thermal correction to Energy	0.104552
Thermal correction to Enthalpy	0.105496
Thermal correction to Gibbs Free Energy	0.072495
Sum of electronic and zero-point Energies	-248.693424
Sum of electronic and thermal Energies	-248.688928
Sum of electronic and thermal Enthalpies	-248.687984
Sum of electronic and thermal Free Energies	-248.720985
E(RB-P86)	-248.793480

Structure:



Coordinates:

C	-0.718309	1.211580	-0.000001	H	-2.509828	0.000036	0.000011
C	-1.418808	0.000017	0.000006	H	-1.236387	-2.169796	0.000013
C	-0.718344	-1.211560	0.000008	H	1.291825	-2.082381	0.000001
C	0.667833	-1.190574	0.000001	H	1.291886	2.082345	-0.000012
C	0.667863	1.190560	-0.000007	N	1.311696	-0.000019	-0.000006
H	-1.236334	2.169826	-0.000001	H	2.335553	-0.000031	-0.000013

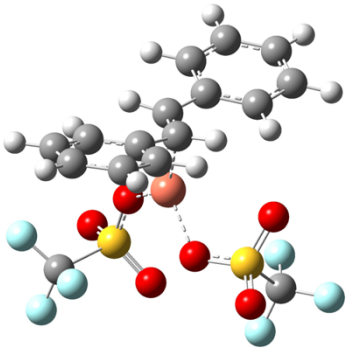
Copper-(I)-OTf$_2$-anion-stilbene adduct (Int-7):

Energies (Hartree):

Zero-point correction	0.261709
Thermal correction to Energy	0.293747
Thermal correction to Enthalpy	0.294691
Thermal correction to Gibbs Free Energy	0.190259
Sum of electronic and zero-point Energies	-2660.717101
Sum of electronic and thermal Energies	-2660.685063
Sum of electronic and thermal Enthalpies	-2660.684119
Sum of electronic and thermal Free Energies	-2660.788551

E(RB-P86) -2660.978810

Structure:



Coordinates:

O	-0.053282	-0.367751	-1.654447	O	3.065022	-2.085384	2.343818
C	-1.910623	0.605153	2.420796	O	1.387378	-0.568311	1.347754
C	-1.682441	0.430518	3.802203	F	4.866323	-1.396586	-0.041641
C	-3.000035	-0.074505	1.830738	C	3.815217	-0.602123	0.270602
C	-2.520658	-0.378349	4.573657	F	4.257597	0.373514	1.100392
H	-0.837944	0.942580	4.271628	F	3.375687	-0.016852	-0.866819
C	-3.834942	-0.881477	2.603822	C	-1.014971	1.503320	1.666351
H	-3.185826	0.013622	0.757417	C	-1.266852	2.013086	0.387965
C	-3.602923	-1.036578	3.978458	C	-0.546476	3.133965	-0.246639
H	-2.326046	-0.496669	5.642330	H	-2.190440	1.718564	-0.120445
H	-4.670740	-1.401603	2.129488	C	-1.061791	3.669604	-1.446324
H	-4.258699	-1.672156	4.578046	C	0.622996	3.713332	0.293516
Cu	-0.063887	0.338535	0.243718	C	-0.443174	4.751918	-2.076814
C	-1.425040	-2.582778	-2.177450	H	-1.961174	3.226770	-1.882450
F	-2.513495	-3.068651	-2.822455	C	1.239722	4.793574	-0.337788
F	-0.330811	-3.202598	-2.668588	H	1.059550	3.319035	1.214162
F	-1.539699	-2.892166	-0.866228	C	0.710985	5.319898	-1.525387
S	-1.310083	-0.711064	-2.420506	H	-0.862436	5.150377	-3.003793
O	-1.149492	-0.546037	-3.871064	H	2.143050	5.227999	0.097300
O	-2.551109	-0.198962	-1.812848	H	1.198698	6.164862	-2.016882
O	2.086380	-2.630660	0.095760	H	-0.216155	1.956332	2.263747
S	2.445541	-1.615915	1.094985				

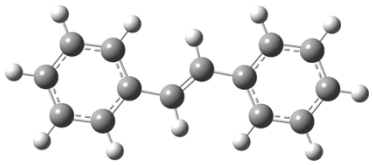
Stilbene (37):

Energies (Hartree):

Zero-point correction	0.207552
Thermal correction to Energy	0.219237

Thermal correction to Enthalpy	0.220181
Thermal correction to Gibbs Free Energy	0.167767
Sum of electronic and zero-point Energies	-540.637849
Sum of electronic and thermal Energies	-540.626165
Sum of electronic and thermal Enthalpies	-540.625220
Sum of electronic and thermal Free Energies	-540.677635
E(RB-P86)	-540.845401

Structure:



Coordinates:

C	-4.747643	0.204452	0.000000	C	0.500221	0.457237	0.000000
C	-4.218355	-1.091167	0.000000	H	0.242121	1.522654	0.000000
C	-2.834213	-1.282778	0.000000	C	1.940516	0.187930	0.000000
C	-1.940516	-0.187930	0.000000	C	2.494713	-1.113371	0.000000
C	-2.494713	1.113371	0.000000	C	3.876212	-1.304254	0.000000
C	-3.876212	1.304254	0.000000	C	4.747643	-0.204452	0.000000
H	-5.829124	0.359204	0.000000	C	4.218355	1.091167	0.000000
H	-4.885764	-1.956563	0.000000	C	2.834213	1.282778	0.000000
H	-2.427645	-2.298402	0.000000	H	1.838824	-1.987102	0.000001
H	-1.838824	1.987102	0.000001	H	4.280257	-2.319786	0.000000
H	-4.280257	2.319786	0.000000	H	5.829124	-0.359204	0.000000
C	-0.500221	-0.457237	0.000000	H	4.885764	1.956563	0.000000
H	-0.242121	-1.522654	0.000000	H	2.427645	2.298402	0.000000

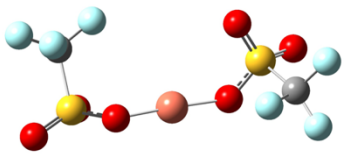
Copper(I) triflate anion (178):

Energies (Hartree):

Zero-point correction	0.207552
Thermal correction to Energy	0.219237
Thermal correction to Enthalpy	0.220181
Thermal correction to Gibbs Free Energy	0.167767
Sum of electronic and zero-point Energies	-540.637849

Sum of electronic and thermal Energies	-540.626165
Sum of electronic and thermal Enthalpies	-540.625220
Sum of electronic and thermal Free Energies	-540.677635
E(RB-P86)	-540.845401

Structure:



Coordinates:

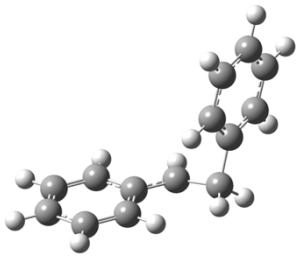
O	-1.631481	-1.035154	0.609335	O	1.682664	-0.468813	-1.093487
C	-3.328998	0.995927	0.333237	S	2.612861	0.653632	-0.630711
F	-4.476060	1.392668	-0.262165	C	3.651078	-0.224044	0.685532
F	-3.478333	1.114180	1.670179	O	1.930358	1.731549	0.095791
F	-2.334876	1.820935	-0.061878	O	3.573674	1.007975	-1.678543
S	-2.940057	-0.792968	-0.145037	F	4.563109	0.631969	1.197798
O	-4.036419	-1.575726	0.431458	F	2.869013	-0.668097	1.695387
O	-2.787123	-0.761513	-1.605338	F	4.305784	-1.280129	0.156455
Cu	0.014191	-0.713524	-0.252978				

Stilbenium cation (601):

Energies (Hartree):

Zero-point correction	0.219575
Thermal correction to Energy	0.231406
Thermal correction to Enthalpy	0.232350
Thermal correction to Gibbs Free Energy	0.180294
Sum of electronic and zero-point Energies	-541.015593
Sum of electronic and thermal Energies	-541.003762
Sum of electronic and thermal Enthalpies	-541.002818
Sum of electronic and thermal Free Energies	-541.054874
E(RB-P86)	-541.235168

Structure:

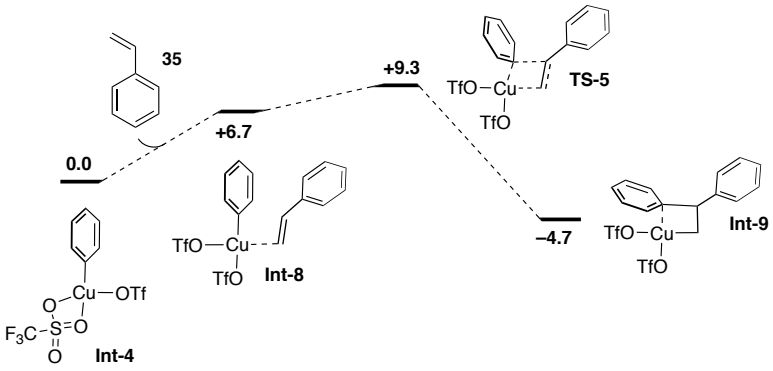


Coordinates:

C	1.728979	-0.390503	0.560687	H	-0.080580	-1.938190	-0.599523
C	1.667915	1.012234	0.462999	C	-2.294122	-0.750309	-1.166635
C	2.792373	-1.088183	-0.042685	C	-2.099147	0.319600	1.047783
C	2.694755	1.713203	-0.172223	C	-3.511497	-0.119334	-1.362877
H	0.828907	1.556975	0.902638	H	-1.878434	-1.410557	-1.930819
C	3.812391	-0.382829	-0.681819	C	-3.315899	0.944907	0.837649
H	2.834051	-2.178506	0.017692	H	-1.560213	0.480850	1.982161
C	3.765445	1.017380	-0.747772	C	-4.019773	0.727566	-0.362996
H	2.655970	2.803060	-0.223906	H	-4.072836	-0.275710	-2.284961
H	4.649843	-0.924671	-1.125990	H	-3.734108	1.602766	1.600777
H	4.562850	1.565786	-1.253757	H	-4.979497	1.225647	-0.517798
C	0.618679	-1.156187	1.307739	H	0.267085	-0.611235	2.190545
C	-0.359500	-1.258873	0.214469	H	0.987922	-2.147928	1.604748
C	-1.560759	-0.546720	0.045380				

i.2.3 Styrene functionalisation towards 1,1-diphenylethylene

Pathway elaborated as below (Scheme 140).



Scheme 140 – Association of styrene **35** to key κ^2-bound copper(III) species **Int-4** and reactions towards 1,1-diphenylethylene production (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Copper(III)-Ph-K²OTf-OTf (Int-4):

See section 1.2.2

Styrene (35):

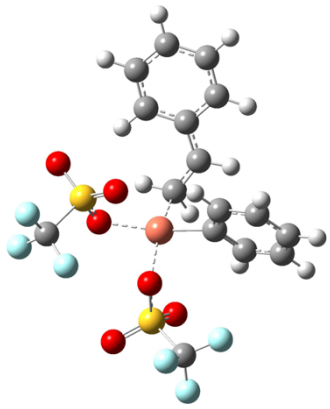
See section 1.2.2

Copper(III)-styrene-Ph-OTf_2 – towards 1,1-diphenylethylene (Int-8):

Energies (Hartree):

Zero-point correction	0.270827
Thermal correction to Energy	0.303587
Thermal correction to Enthalpy	0.304531
Thermal correction to Gibbs Free Energy	0.198982
Sum of electronic and zero-point Energies	-2661.049935
Sum of electronic and thermal Energies	-2661.017175
Sum of electronic and thermal Enthalpies	-2661.016231
Sum of electronic and thermal Free Energies	-2661.121780
E(RB-P86)	-2661.320762

Structure:



Coordinates:

C	-0.112144	-1.992931	0.175057	H	3.557589	0.745293	-1.327252
C	0.428268	-2.076122	1.451180	C	6.118102	-0.763859	0.338100
C	-0.809568	-3.010039	-0.454805	H	6.186721	-2.835200	0.974590
C	0.178764	-3.256862	2.174634	H	5.792186	1.247130	-0.403393
H	1.006723	-1.264019	1.896945	O	0.444557	1.737998	-1.070111
C	-1.036853	-4.182343	0.288388	S	1.185925	2.322190	0.122749
H	-1.216010	-2.905462	-1.461602	C	0.016785	3.669451	0.760777
C	-0.542168	-4.302859	1.591197	O	2.401448	3.052410	-0.244637
H	0.568185	-3.343318	3.191794	O	1.271559	1.322367	1.211278
H	-1.609439	-4.993255	-0.168025	F	0.636364	4.360402	1.742988
H	-0.713692	-5.223160	2.153914	F	-0.294945	4.522071	-0.236648
Cu	0.017962	-0.215063	-0.563351	F	-1.114294	3.140195	1.254244
C	1.389904	-0.922203	-1.923719	O	-1.777896	0.281940	0.161596
C	2.310637	-1.728385	-1.229215	S	-2.960646	0.203429	-0.805778
H	0.651293	-1.445831	-2.541548	O	-2.702261	-0.687613	-1.946894
C	3.582523	-1.352662	-0.701930	O	-3.565243	1.511186	-1.066375
H	2.040485	-2.779680	-1.092427	C	-4.238741	-0.690340	0.265822
C	4.346833	-2.356575	-0.042165	F	-5.392770	-0.814118	-0.425433
C	4.123417	-0.042107	-0.827301	F	-3.809786	-1.921341	0.608197
C	5.603323	-2.062944	0.470671	F	-4.483200	0.010837	1.391479
H	3.930710	-3.362075	0.054159	H	7.105676	-0.529958	0.741946
C	5.378130	0.242025	-0.309652	H	1.701294	0.060265	-2.288017

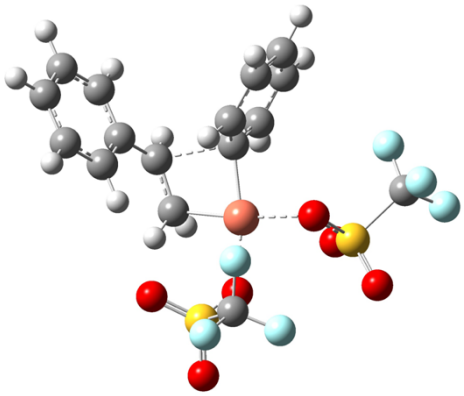
Copper(III)-styrene-Ph-OTf$_2$ – TS – towards 1,1-diphenylethylene (TS-9):

Energies (Hartree):

Zero-point correction	0.270803
Thermal correction to Energy	0.302735
Thermal correction to Enthalpy	0.303679

Thermal correction to Gibbs Free Energy	0.201471
Sum of electronic and zero-point Energies	-2661.048329
Sum of electronic and thermal Energies	-2661.016397
Sum of electronic and thermal Enthalpies	-2661.015453
Sum of electronic and thermal Free Energies	-2661.117661
E(RB-P86)	-2661.319132

Structure:



Coordinates:

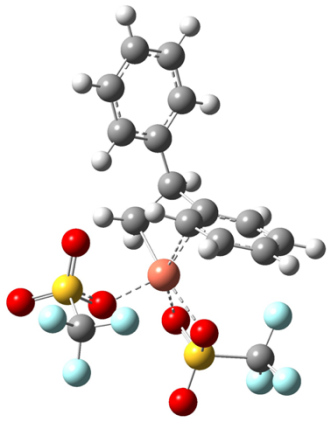
C	0.747983	-1.707269	-0.233481	H	3.328195	1.046078	0.118433
C	1.161323	-1.759057	1.107292	C	6.049118	-0.870637	0.862390
C	0.185158	-2.807546	-0.901255	H	6.408431	-2.888729	0.159910
C	0.927963	-2.935428	1.820685	H	5.439775	1.137588	1.401084
H	1.654206	-0.910302	1.586154	O	-0.535673	1.917278	-1.060517
C	-0.018868	-3.980551	-0.171101	S	0.215696	3.174314	-0.649775
H	-0.101325	-2.751121	-1.952516	C	-0.286352	3.386317	1.161272
C	0.348784	-4.040863	1.180078	O	-0.307618	4.359018	-1.329047
H	1.215385	-2.991627	2.872319	O	1.677915	2.994879	-0.594614
H	-0.463162	-4.847895	-0.663031	F	0.312389	4.483042	1.673512
H	0.196192	-4.966684	1.738641	F	-1.618766	3.524537	1.280646
Cu	-0.039753	0.027653	-0.637774	F	0.104805	2.309847	1.884084
C	1.607337	0.007561	-1.754627	O	-1.744221	-0.224584	0.460044
C	2.453939	-1.095056	-1.400176	S	-3.015774	-0.276069	-0.373613
H	1.062031	-0.092014	-2.702471	O	-2.745238	-0.647594	-1.773927
C	3.654649	-0.993670	-0.592869	O	-3.939750	0.831321	-0.116503
H	2.393653	-1.987981	-2.026026	C	-3.888725	-1.775773	0.377825
C	4.537051	-2.099907	-0.567519	F	-5.092130	-1.945226	-0.213503
C	3.991120	0.177558	0.128452	F	-3.165244	-2.902955	0.198033
C	5.728209	-2.035053	0.150730	F	-4.083560	-1.600240	1.702702
H	4.277847	-3.004693	-1.123048	H	6.981790	-0.819340	1.428485
C	5.180795	0.232205	0.848992	H	1.923399	1.022307	-1.481163

1,1-diphenylethyl-Copper(III)-OTf$_2$ (Int-9):

Energies (Hartree):

Zero-point correction	0.272424
Thermal correction to Energy	0.304487
Thermal correction to Enthalpy	0.305431
Thermal correction to Gibbs Free Energy	0.202795
Sum of electronic and zero-point Energies	-2661.070248
Sum of electronic and thermal Energies	-2661.038185
Sum of electronic and thermal Enthalpies	-2661.037241
Sum of electronic and thermal Free Energies	-2661.139877
E(RB-P86)	-2661.342672

Structure:



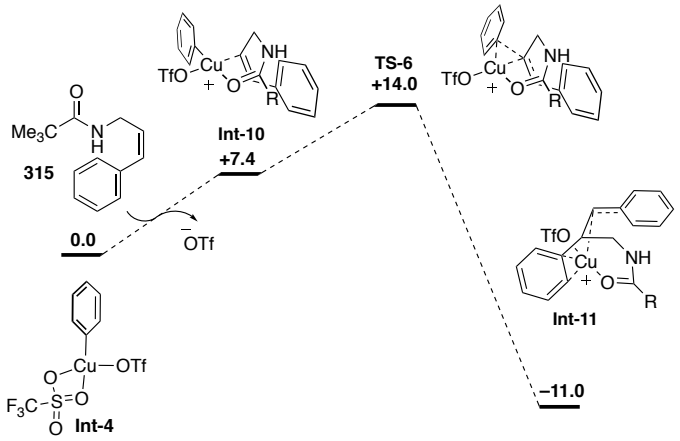
Coordinates:

C	1.110231	-1.577769	0.476508	H	3.594423	0.646698	-0.383324
C	1.208132	-0.459799	1.371525	C	6.246668	-1.480197	-0.149024
C	0.323371	-2.700198	0.855697	H	6.150136	-3.631899	-0.382626
C	0.572104	-0.509034	2.622405	H	6.023864	0.666570	0.015970
H	1.856460	0.385385	1.128315	O	-0.445692	1.800279	-1.013733
C	-0.274616	-2.734233	2.106340	S	0.477142	2.961044	-0.656581
H	0.233923	-3.545738	0.171514	C	-0.436651	3.776769	0.787695
C	-0.153201	-1.640978	2.989136	O	0.492555	3.982309	-1.704505
H	0.662118	0.337357	3.304368	O	1.763675	2.522929	-0.087231
H	-0.841405	-3.615696	2.410626	F	0.261657	4.850299	1.214489
H	-0.634568	-1.683825	3.967986	F	-1.662150	4.180719	0.403184
Cu	-0.251418	-0.090935	-0.333101	F	-0.568206	2.913484	1.817839
C	1.315709	-0.473562	-1.548840	O	-2.131167	-0.194238	0.623832
C	1.965578	-1.604091	-0.819708	S	-2.913298	-0.539971	-0.624177
H	0.655312	-0.711532	-2.391131	O	-1.920975	-0.799454	-1.717589
C	3.467867	-1.519254	-0.595395	O	-4.057382	0.311115	-0.930185
H	1.729496	-2.551126	-1.326995	C	-3.680697	-2.230941	-0.250465

C	4.209015	-2.712728	-0.602749	F	-4.495645	-2.588234	-1.261319
C	4.135377	-0.303241	-0.374016	F	-2.726197	-3.173194	-0.111997
C	5.588608	-2.694906	-0.376480	F	-4.397065	-2.166544	0.888461
H	3.701660	-3.664173	-0.785528	H	7.325455	-1.463854	0.021272
C	5.517419	-0.286662	-0.150930	H	1.803619	0.504440	-1.569236

i.2.4 Functionalisation of allylic amide 315 towards oxazine formation

Pathway elaborated as below (Scheme 142).



Scheme 142 – Reaction of amide **315** with **Int-4** towards oxazine formation (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Copper(III)-Ph-K^{2}OTf-OTf (Int-4):

See section 1.2.1

Allylic amide substrate (315):

Energies (Hartree):

Zero-point correction	0.292655
Thermal correction to Energy	0.309583
Thermal correction to Enthalpy	0.310528
Thermal correction to Gibbs Free Energy	0.246166
Sum of electronic and zero-point Energies	-674.661591
Sum of electronic and thermal Energies	-674.644663
Sum of electronic and thermal Enthalpies	-674.643719
Sum of electronic and thermal Free Energies	-674.708081
E(RB-P86)	-674.954247

Structure:

Coordinates:

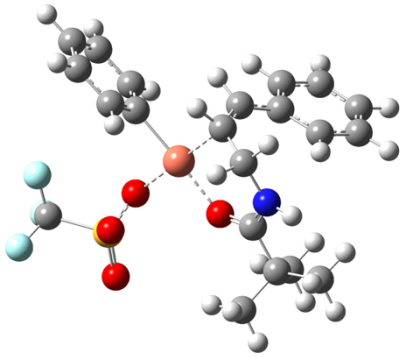
C	-3.042341	-0.543255	-0.309821	O	2.617029	1.146544	-1.341943
C	-4.153580	-1.175270	0.306478	C	3.881970	-0.013731	0.393696
C	-5.229838	-0.427930	0.806416	C	4.814741	-0.688429	-0.644319
C	-5.232256	0.974540	0.686459	H	4.989771	-0.019265	-1.501827
C	-4.154684	1.616131	0.050628	H	5.786724	-0.922960	-0.176090
C	-3.074376	0.868121	-0.446263	H	4.379950	-1.631072	-1.021095
H	-4.160225	-2.267482	0.399806	C	4.534854	1.296879	0.903132
H	-6.070753	-0.940048	1.286027	H	3.897280	1.796604	1.653742
H	-4.159585	2.704347	-0.072626	H	5.506484	1.070588	1.376314
H	-2.271683	1.382530	-0.982412	H	4.704942	1.997333	0.069888
C	-1.935384	-1.385205	-0.804264	C	3.663187	-0.972414	1.585163
H	-2.232938	-2.399815	-1.102976	H	4.637125	-1.203448	2.049952
C	-0.613277	-1.090460	-0.906092	H	3.030924	-0.524208	2.372979
H	0.047494	-1.866249	-1.315685	H	3.220840	-1.935316	1.271868
C	0.096934	0.172025	-0.482295	N	1.400932	-0.129615	0.116492
H	0.312692	0.827834	-1.346131	H	1.416239	-0.736507	0.934451
H	-0.512308	0.753893	0.232981	H	-6.074023	1.559889	1.070586
C	2.578764	0.383716	-0.352194				

Cu(III)-OTf-bidentatesubstrate-cation (Int-10):

Energies (Hartree):

Zero-point correction	0.410544
Thermal correction to Energy	0.443545
Thermal correction to Enthalpy	0.444489
Thermal correction to Gibbs Free Energy	0.342520
Sum of electronic and zero-point Energies	-2063.187774
Sum of electronic and thermal Energies	-2063.154774
Sum of electronic and thermal Enthalpies	-2063.153830
Sum of electronic and thermal Free Energies	-2063.255799
E(RB-P86)	-2063.598319

Structure:



Coordinates:

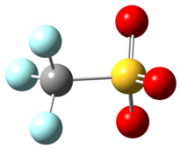
C	-1.460330	1.854180	0.476812	H	1.420773	-4.212634	1.355941
C	-1.620738	2.728838	-0.597416	H	0.794102	-3.845857	-0.281942
C	-2.195599	1.916218	1.659313	C	1.128546	1.195189	1.669464
C	-2.587720	3.750917	-0.458808	H	2.504256	0.547741	3.156185
H	-1.054156	2.638353	-1.529353	H	0.974269	-0.341332	3.136674
C	-3.157512	2.947493	1.768931	C	1.618764	1.992368	0.603752
H	-2.069046	1.201207	2.477270	H	0.374183	1.722975	2.269470
C	-3.345543	3.859031	0.718624	C	2.805458	1.960079	-0.212910
H	-2.739209	4.447579	-1.290006	H	0.955722	2.838079	0.377643
H	-3.749820	3.017629	2.687350	C	2.823065	2.833900	-1.345152
H	-4.091154	4.654600	0.814868	C	3.981392	1.212278	0.092345
Cu	-0.184098	0.365764	0.263859	C	3.951643	2.922298	-2.160967
O	1.037078	-1.169826	-0.013976	H	1.934368	3.432248	-1.570828
C	2.017995	-1.616364	0.660215	C	5.114007	1.323229	-0.715629
C	2.729220	-2.886456	0.163579	H	4.009115	0.571109	0.973739
N	2.440296	-1.015199	1.787780	C	5.099058	2.165823	-1.847581
C	3.087882	-2.680562	-1.331090	H	3.949111	3.583750	-3.031808
C	4.003966	-3.215720	0.970596	H	6.017923	0.760249	-0.466178
C	1.705004	-4.048594	0.302290	O	-1.477151	-0.463692	-0.966941
C	1.759360	0.081230	2.483901	S	-2.275871	-1.684746	-0.411045
H	3.193529	-1.472999	2.303983	O	-2.186873	-1.769929	1.071954
H	3.811446	-1.858079	-1.462422	O	-2.058769	-2.904173	-1.224623
H	3.545190	-3.604858	-1.721529	C	-4.059392	-1.152905	-0.805199
H	2.188796	-2.456597	-1.925512	F	-4.909598	-2.130954	-0.417171
H	3.788819	-3.442446	2.030541	F	-4.373214	-0.015157	-0.149259
H	4.465233	-4.122482	0.546397	F	-4.202864	-0.948527	-2.133495
H	4.756936	-2.410385	0.912770	H	5.989825	2.241439	-2.478960
H	2.166136	-4.976247	-0.076340				

OTf-anion:

Energies (Hartree):

Zero-point correction	0.025017
Thermal correction to Energy	0.032531
Thermal correction to Enthalpy	0.033476
Thermal correction to Gibbs Free Energy	-0.007799
Sum of electronic and zero-point Energies	-961.652226
Sum of electronic and thermal Energies	-961.644712
Sum of electronic and thermal Enthalpies	-961.643768
Sum of electronic and thermal Free Energies	-961.685042
E(RB-P86)	-961.677243

Structure:



Coordinates:

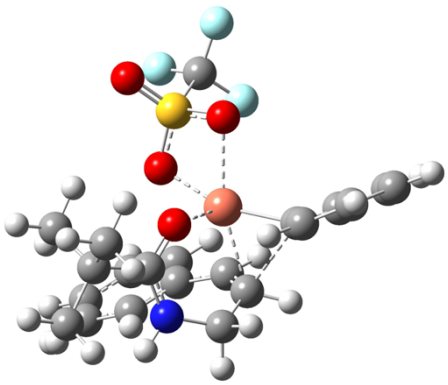
C	-0.970231	-0.000043	0.000289	S	0.933938	0.000092	-0.000123
F	-1.465715	0.951635	0.841286	O	1.267916	1.387948	-0.462747
F	-1.465164	0.252599	-1.244569	O	1.269558	-0.293086	1.432696
F	-1.465334	-1.204556	0.403676	O	1.268064	-1.094650	-0.970361

Cu(III)-OTf-bidentatesubstrate-cation – TS – towards oxazine (TS-6):

Energies (Hartree):

Zero-point correction	0.409431
Thermal correction to Energy	0.441760
Thermal correction to Enthalpy	0.442704
Thermal correction to Gibbs Free Energy	0.344213
Sum of electronic and zero-point Energies	-2063.180054
Sum of electronic and thermal Energies	-2063.147726
Sum of electronic and thermal Enthalpies	-2063.146781
Sum of electronic and thermal Free Energies	-2063.245272
E(RB-P86)	-2063.589485

Structure:



Coordinates:

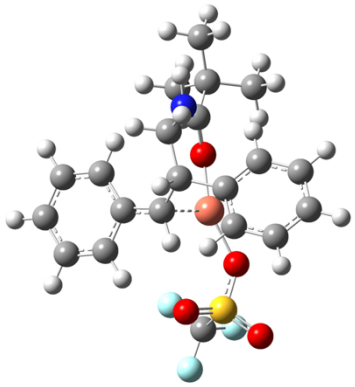
C	-0.891897	2.215192	-1.151408	H	3.692802	2.919867	2.31286
C	-2.063645	2.14184	-1.916206	H	2.351915	2.10452	3.177786
C	-0.459499	3.373775	-0.497707	C	0.746037	0.97317	-2.048537
C	-2.895423	3.279181	-1.943245	H	2.741913	1.332745	-2.623406
H	-2.352972	1.242613	-2.468032	H	2.020571	2.624216	-1.658291
C	-1.309201	4.498048	-0.547562	C	0.256126	-0.376255	-2.170259
H	0.466986	3.404145	0.080272	H	0.306879	1.6069	-2.830742
C	-2.516145	4.45073	-1.266063	C	0.857533	-1.677853	-2.024842
H	-3.831141	3.237634	-2.509496	H	-0.736113	-0.416578	-2.642555
H	-1.013271	5.405978	-0.012395	C	0.035947	-2.793278	-2.386117
H	-3.158348	5.335603	-1.309094	C	2.208584	-1.922296	-1.635997
Cu	-0.367723	0.539923	-0.248144	C	0.544415	-4.091718	-2.361769
O	1.242937	1.161259	0.992094	H	-1.001415	-2.617284	-2.688711
C	2.464863	1.014144	0.713379	C	2.709236	-3.224184	-1.617635
C	3.483477	0.770402	1.843236	H	2.851278	-1.090143	-1.346052
N	2.901401	1.044098	-0.573676	C	1.882708	-4.31026	-1.976903
C	3.048789	-0.522093	2.584351	H	-0.093314	-4.935173	-2.640629
C	4.937517	0.621962	1.34474	H	3.747351	-3.402682	-1.323005
C	3.382102	1.983359	2.807879	O	-0.562183	-1.313206	0.671879
C	2.12746	1.527096	-1.724904	S	-1.603758	-0.857762	1.709635
H	3.911373	1.009445	-0.718263	O	-1.865598	0.609943	1.425873
H	3.104022	-1.402595	1.921552	O	-1.369246	-1.27567	3.10628
H	3.723031	-0.691938	3.440637	C	-3.196595	-1.754881	1.182269
H	2.018354	-0.43272	2.961608	F	-4.222092	-1.354652	1.963205
H	5.303842	1.532125	0.835863	F	-3.488585	-1.469228	-0.107862
H	5.597064	0.458944	2.213284	F	-3.035831	-3.089448	1.309578
H	5.067618	-0.249189	0.677546	H	2.284474	-5.328074	-1.956993
H	4.04836	1.81425	3.670541				

Cu(I)-OTf-anion-arylatedallylicamide-cation-adduct – towards oxazine (Int-11):

Energies (Hartree):

Zero-point correction	0.412258
Thermal correction to Energy	0.444645
Thermal correction to Enthalpy	0.445589
Thermal correction to Gibbs Free Energy	0.346118
Sum of electronic and zero-point Energies	-2063.218800
Sum of electronic and thermal Energies	-2063.186413
Sum of electronic and thermal Enthalpies	-2063.185469
Sum of electronic and thermal Free Energies	-2063.284940
E(RB-P86)	-2063.631058

Structure:



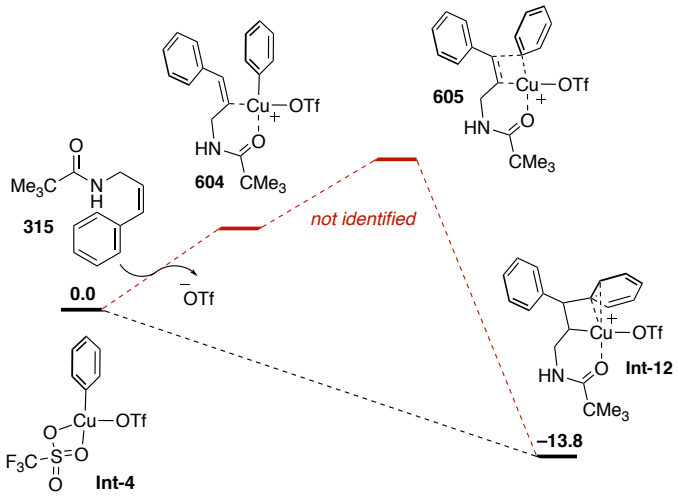
Coordinates:

C	0.784228	2.112225	-1.488945	H	3.937763	1.609069	2.512371
C	-0.396012	2.703988	-1.991678	H	2.798629	0.450404	3.265536
C	1.594483	2.857254	-0.606266	C	1.149833	0.687161	-1.952760
C	-0.770284	3.999773	-1.606007	H	2.825231	-0.553851	-2.541252
H	-1.027092	2.155320	-2.700640	H	3.178108	1.170699	-2.406806
C	1.219139	4.158431	-0.221836	C	0.111370	-0.317933	-1.479444
H	2.530457	2.444401	-0.220074	H	0.947278	0.684576	-3.051397
C	0.036296	4.730904	-0.715013	C	0.147081	-1.760357	-1.489405
H	-1.688549	4.439596	-2.007382	H	-0.910047	0.074687	-1.627269
H	1.860509	4.721756	0.463315	C	-1.125298	-2.416473	-1.619422
H	-0.253392	5.742467	-0.413758	C	1.325940	-2.570991	-1.420034
Cu	-0.004655	0.174788	0.551627	C	-1.203988	-3.803823	-1.734651
O	1.763275	-0.261765	0.998839	H	-2.031206	-1.802795	-1.646894
C	2.977608	-0.173789	0.614384	C	1.233452	-3.955836	-1.531663
C	4.054471	-0.437539	1.687036	H	2.305910	-2.121341	-1.258225
N	3.363463	0.120808	-0.634388	C	-0.026606	-4.576612	-1.694493
C	3.842311	-1.891817	2.190821	H	-2.177163	-4.288405	-1.852732
C	5.495466	-0.278658	1.155833	H	2.139106	-4.566770	-1.482033

C	3.810636	0.565158	2.847403	O	-1.730527	0.874354	0.919224
C	2.649735	0.337696	-1.914655	S	-3.155441	0.678790	0.333802
H	4.378596	0.138927	-0.758762	O	-3.134343	0.178642	-1.068472
H	4.005215	-2.624554	1.381480	O	-4.023765	1.825839	0.674240
H	4.567754	-2.102951	2.993884	C	-3.801186	-0.771525	1.383732
H	2.826502	-2.028406	2.592973	F	-5.055782	-1.087825	0.996140
H	5.704550	0.745757	0.799689	F	-3.006233	-1.857682	1.221898
H	6.197619	-0.476368	1.982127	F	-3.813584	-0.433262	2.690878
H	5.736556	-1.004120	0.357999	H	-0.086030	-5.666265	-1.776893
H	4.542734	0.371957	3.648928				

i.2.5 Functionalisation of allylic amide 315 towards enamide formation

Pathway elaborated as below (Scheme 144).



Scheme 144 – Reaction of amide **315** with **Int-4** towards enamide formation (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Copper(III)-Ph-K^{2}OTf-OTf (Int-4):

See section 1.2.1

Allylic amide substrate (315):

See section 1.2.4

OTf-anion:

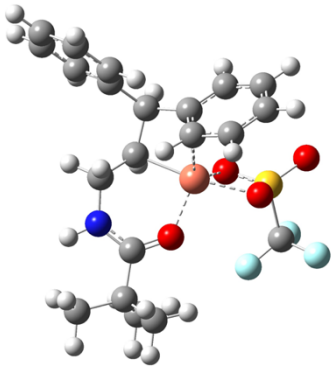
See section 1.2.4

Cu(III)-OTf-arylatedallylicamideadduct-cation – towards enamide (Int-12):

Energies (Hartree):

Zero-point correction	0.411537
Thermal correction to Energy	0.44392
Thermal correction to Enthalpy	0.444864
Thermal correction to Gibbs Free Energy	0.344351
Sum of electronic and zero-point Energies	-2063.222241
Sum of electronic and thermal Energies	-2063.189859
Sum of electronic and thermal Enthalpies	-2063.188915
Sum of electronic and thermal Free Energies	-2063.289427
E(RB-P86)	-2063.633778

Structure:



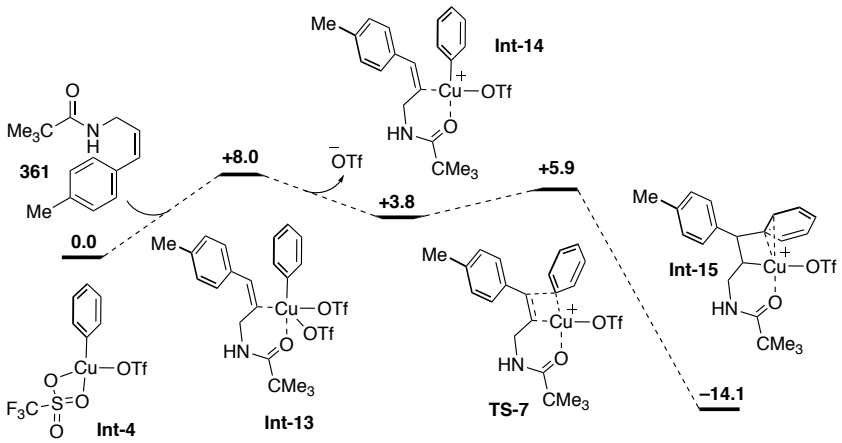
Coordinates:

O	-1.833488	-1.370850	0.880143	H	1.022408	3.908556	-0.199613
C	1.600256	-1.506887	0.290469	H	-1.399972	3.738431	2.723059
C	1.428297	-1.021323	1.632571	H	-2.853136	4.556585	2.085135
C	1.275542	-2.863614	0.005735	H	-2.701214	2.779285	1.953085
C	0.964335	-1.886400	2.645986	H	-0.286205	5.494410	-0.496096
H	1.760765	-0.014871	1.908249	H	-1.445655	6.082007	0.701051
C	0.825659	-3.706945	1.023236	H	0.060623	5.334967	1.267946
H	1.397073	-3.240830	-1.014307	H	-3.260436	4.724965	-0.430501
C	0.664289	-3.219819	2.341189	H	-2.101942	4.020504	-1.593189
H	0.850254	-1.509067	3.665867	H	-3.116680	2.948961	-0.577593
H	0.591756	-4.750953	0.795923	C	1.297001	0.618686	-0.842781
H	0.303838	-3.890768	3.126451	H	2.300600	1.773105	0.700295
Cu	-0.216217	-0.213301	0.224661	H	2.512243	2.329282	-0.958438
C	-3.994439	-1.018272	-0.740907	C	2.214121	-0.605321	-0.800968
F	-4.476604	-1.320871	-1.966118	H	0.669631	0.716352	-1.744828
F	-4.849865	-1.478024	0.197595	C	3.707991	-0.304659	-0.683645
F	-3.894771	0.323287	-0.626670	H	2.051632	-1.134858	-1.756000

S	-2.293354	-1.836108	-0.509621	C	4.367348	0.169540	-1.842318
O	-2.548325	-3.283948	-0.661270	C	4.450049	-0.482329	0.501355
O	-1.383029	-1.166706	-1.523703	C	5.738296	0.464335	-1.813119
O	-1.023483	1.554369	0.455596	H	3.803400	0.290234	-2.774603
C	-0.543858	2.722313	0.283794	C	5.826683	-0.194540	0.527081
C	-1.475956	3.925278	0.525281	H	3.970235	-0.862051	1.408424
N	0.719736	2.937025	-0.118104	C	6.472198	0.285547	-0.625087
C	-2.146241	3.728850	1.910370	H	6.235975	0.823495	-2.719537
C	-0.724777	5.274291	0.493953	H	6.392404	-0.346880	1.451642
C	-2.553546	3.894436	-0.594469	H	7.542584	0.513093	-0.600843
C	1.760649	1.916479	-0.255307				

i.2.6 Functionalisation of allylic amide 361 towards enamide formation

Pathway elaborated as below (Scheme 145).



Scheme 145 – Reactivity of amide **361** with **Int-4** towards enamide formation (Gaussian 09 - BP86 functional, Def2QZVP (SDD) [Cu], 6-311G+(2d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Copper(III)-Ph-K^{2}OTf-OTf (Int-4):

See section 1.2.2

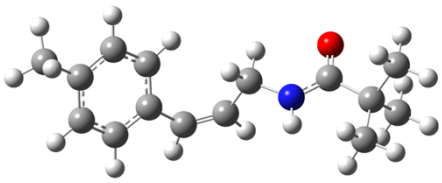
Allylic amide substrate (361):

Energies (Hartree):

Zero-point correction	0.317955
Thermal correction to Energy	0.336839
Thermal correction to Enthalpy	0.337783
Thermal correction to Gibbs Free Energy	0.268364
Sum of electronic and zero-point Energies	-714.113647
Sum of electronic and thermal Energies	-714.094764
Sum of electronic and thermal Enthalpies	-714.093819
Sum of electronic and thermal Free Energies	-714.163238

E(RB-P86) -714.4316021

Structure:



Coordinates:

C	2.542929	0.903900	-0.259240	C	-4.251502	-0.236757	0.450598
C	3.613481	1.404747	0.514351	C	-5.209702	0.798828	-0.183009
C	4.745953	0.633061	0.773583	H	-5.436887	0.532266	-1.224782
C	4.873071	-0.669579	0.257291	H	-6.153337	0.831146	0.384466
C	3.827512	-1.157041	-0.544485	H	-4.769893	1.808855	-0.170824
C	2.686767	-0.390920	-0.801398	C	-4.907284	-1.636191	0.421147
H	3.545883	2.417448	0.922682	H	-4.253417	-2.393302	0.882686
H	5.553171	1.051342	1.382291	H	-5.855249	-1.616577	0.981845
H	3.913235	-2.152469	-0.990377	H	-5.117384	-1.944121	-0.612569
H	1.921211	-0.789531	-1.469889	C	-3.961666	0.161255	1.911030
C	1.368613	1.762654	-0.483650	H	-4.904024	0.172296	2.480118
H	1.584747	2.837725	-0.476220	H	-3.291344	-0.556199	2.411884
C	0.075648	1.412632	-0.657126	H	-3.528189	1.171807	1.990296
H	-0.650143	2.218512	-0.814237	N	-1.798662	0.035487	0.117319
C	-0.528601	0.034389	-0.611799	H	-1.782724	0.315911	1.094404
H	-0.766721	-0.335061	-1.623334	C	6.088382	-1.513264	0.559335
H	0.159263	-0.688952	-0.145421	H	6.256634	-2.270558	-0.220361
C	-2.991062	-0.300919	-0.451446	H	6.995398	-0.896291	0.645381
O	-3.079096	-0.644297	-1.642125	H	5.967948	-2.049043	1.516616

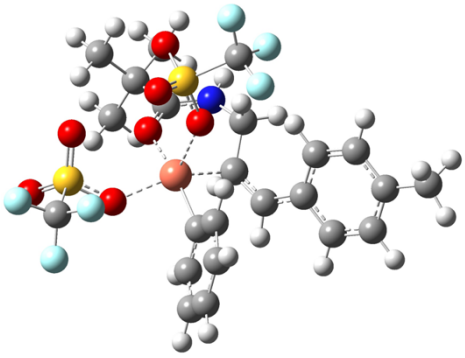
Cu(III)-OTf$_2$-bidentateallylicamideadduct – towards enamide (Int-13):

Energies (Hartree):

Zero-point correction	0.460277
Thermal correction to Energy	0.504995
Thermal correction to Enthalpy	0.505939
Thermal correction to Gibbs Free Energy	0.375937

Sum of electronic and zero-point Energies	-3065.569251
Sum of electronic and thermal Energies	-3065.524533
Sum of electronic and thermal Enthalpies	-3065.523589
Sum of electronic and thermal Free Energies	-3065.653591
E(RB-P86)	-3066.029528

Structure:



Coordinates:

O	0.467266	0.473531	1.123759	H	-2.813600	5.768969	-2.219419
C	0.400020	-1.847958	-1.070948	H	-1.358477	5.537356	-1.238362
C	1.144551	-2.307656	0.006734	H	-4.147959	3.806228	-3.094867
C	0.014694	-2.648930	-2.143585	H	-2.691210	3.064855	-3.805751
C	1.436631	-3.681244	0.053595	H	-3.697948	2.135669	-2.657063
H	1.459593	-1.639728	0.809754	C	0.889958	0.835790	-2.038198
C	0.322725	-4.016689	-2.078023	H	1.218012	2.088437	-0.289532
H	-0.533446	-2.252580	-3.000768	H	1.954149	2.684436	-1.800647
C	1.031659	-4.527243	-0.984521	C	1.925710	-0.120269	-2.194536
H	1.984449	-4.076059	0.912560	H	0.201874	0.848346	-2.896825
H	0.009189	-4.671284	-2.894696	C	3.230218	-0.211931	-1.612172
H	1.282319	-5.589847	-0.948541	H	1.757939	-0.824255	-3.012749
Cu	-0.527615	-0.127587	-0.868476	C	4.141471	-1.115454	-2.225731
C	1.819494	1.531646	3.115329	C	3.687744	0.543495	-0.497995
F	1.726517	2.086643	4.344986	C	5.447742	-1.231853	-1.772850
F	2.655467	0.468815	3.196063	H	3.803812	-1.716360	-3.073721
F	2.393222	2.448619	2.288010	C	4.990570	0.408257	-0.046695
S	0.112227	1.020694	2.478906	H	3.011108	1.209115	0.034856
O	-0.321926	0.005315	3.448807	C	5.900213	-0.472788	-0.675371
O	-0.635542	2.287646	2.446778	H	6.132499	-1.925649	-2.265954
O	-1.651394	1.524468	-1.050904	H	5.321698	0.988578	0.817764
C	-1.350060	2.690256	-1.431048	C	7.310240	-0.593251	-0.172685
C	-2.478755	3.694901	-1.705303	H	7.844101	0.364839	-0.288904

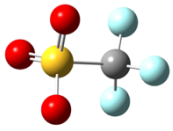
N	-0.076565	3.059713	-1.634317	H	7.322240	-0.830316	0.903268
C	-3.362988	3.765485	-0.438484	H	7.871155	-1.368811	-0.710434
C	-1.955323	5.100998	-2.055189	O	-2.249668	-1.208251	-0.745790
C	-3.301562	3.133021	-2.891473	S	-3.436540	-1.136060	0.203009
C	1.067110	2.188127	-1.374605	C	-3.362947	-2.848855	1.003040
H	0.109080	4.020229	-1.912490	O	-4.710427	-1.146035	-0.529916
H	-2.800320	4.160874	0.420361	O	-3.281728	-0.198200	1.316354
H	-4.214626	4.435519	-0.630989	F	-4.384596	-2.991614	1.878878
H	-3.749030	2.772927	-0.172294	F	-3.467201	-3.822623	0.069244
H	-1.362400	5.111098	-2.984754	F	-2.202934	-3.022018	1.670281

OTf-anion:

Energies (Hartree):

Zero-point correction	0.025114
Thermal correction to Energy	0.032588
Thermal correction to Enthalpy	0.033532
Thermal correction to Gibbs Free Energy	-0.007672
Sum of electronic and zero-point Energies	-961.876919
Sum of electronic and thermal Energies	-961.869445
Sum of electronic and thermal Enthalpies	-961.868501
Sum of electronic and thermal Free Energies	-961.909705
E(RB-P86)	-961.902033

Structure:



Coordinates:

C	0.962162	0.000063	-0.000023	S	-0.930667	0.000049	0.000043
F	1.457249	0.846719	0.940631	O	-1.259053	-0.443147	1.373792
F	1.456744	-1.238106	0.262916	O	-1.259343	1.411300	-0.303057
F	1.456937	0.391249	-1.203709	O	-1.259187	-0.968143	-1.070622

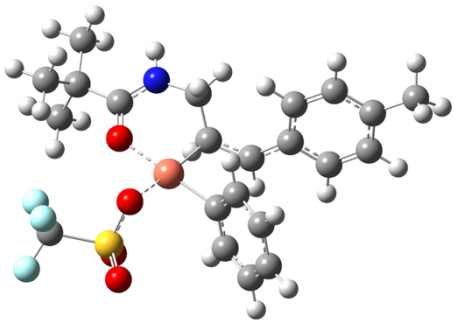
Cu(III)-OTf-bidentateallylicamideadduct-cation – towards enamide (Int-14):

Energies (Hartree):

Zero-point correction	0.434613
Thermal correction to Energy	0.469737
Thermal correction to Enthalpy	0.470682
Thermal correction to Gibbs Free Energy	0.362896

Sum of electronic and zero-point Energies	-2103.678829
Sum of electronic and thermal Energies	-2103.643705
Sum of electronic and thermal Enthalpies	-2103.642761
Sum of electronic and thermal Free Energies	-2103.750546
E(RB-P86)	-2104.113442

Structure:



Coordinates:

O	1.587513	-1.218187	-0.807101	H	3.045583	3.574798	-2.055011
C	-1.045891	-1.408331	0.206919	H	4.452756	3.959320	-1.031445
C	-1.698155	-1.702417	-0.988816	H	3.840026	2.284517	-1.109071
C	-1.052387	-2.255738	1.313873	H	1.598352	5.417310	0.949006
C	-2.314534	-2.955391	-1.107083	H	3.142852	5.752379	0.156732
H	-1.716718	-1.001448	-1.827182	H	1.722325	5.429497	-0.845325
C	-1.681210	-3.502970	1.175198	H	4.263989	3.941868	1.503823
H	-0.562588	-1.992060	2.252404	H	2.725625	3.528388	2.302117
C	-2.310250	-3.846401	-0.025980	H	3.660637	2.262910	1.455379
H	-2.799506	-3.224930	-2.047924	C	-1.092922	1.302681	0.800322
H	-1.677550	-4.195948	2.019477	H	-1.099335	2.069915	-1.254027
H	-2.812811	-4.811625	-0.117986	H	-1.878259	3.118250	-0.053420
Cu	0.276775	0.002250	0.097125	C	-2.300228	0.594298	1.109797
C	4.195440	-1.638736	-0.490600	H	-0.507718	1.499958	1.713331
F	5.097851	-2.425250	0.134113	C	-3.589743	0.603095	0.507028
F	4.307320	-1.827295	-1.822204	H	-2.263543	0.071383	2.069090
F	4.482995	-0.351899	-0.210532	C	-4.641786	-0.016416	1.245756
S	2.454010	-2.094152	0.099047	C	-3.916504	1.201110	-0.744569
O	2.337565	-3.520701	-0.211200	C	-5.944014	-0.011436	0.776382
O	2.390744	-1.671380	1.506743	H	-4.409247	-0.486976	2.203943
O	1.607846	1.465695	-0.008208	C	-5.220447	1.189051	-1.207592
C	1.416165	2.717491	0.006927	H	-3.146803	1.655570	-1.366263
C	2.626303	3.653252	0.105757	C	-6.261706	0.588171	-0.461338

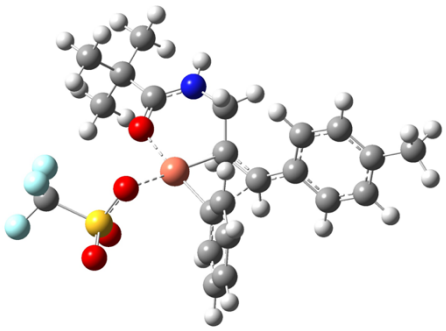
N	0.182284	3.235909	-0.056053	H	-6.735370	-0.478096	1.367062
C	3.544784	3.341921	-1.101851	H	-5.453702	1.652034	-2.169001
C	2.230697	5.142043	0.089323	C	-7.664291	0.564870	-0.989433
C	3.360530	3.318818	1.427432	H	-7.866845	1.427793	-1.639077
C	-1.029006	2.435923	-0.215096	H	-7.817147	-0.343739	-1.599062
H	0.082996	4.248710	-0.058910	H	-8.402534	0.537290	-0.176059

Cu(III)-OTf-bidentateallylicamideadduct-cation – TS – towards enamide (TS-7):

Energies (Hartree):

Zero-point correction	0.435307
Thermal correction to Energy	0.469461
Thermal correction to Enthalpy	0.470406
Thermal correction to Gibbs Free Energy	0.365591
Sum of electronic and zero-point Energies	-2103.677504
Sum of electronic and thermal Energies	-2103.643350
Sum of electronic and thermal Enthalpies	-2103.642405
Sum of electronic and thermal Free Energies	-2103.747220
E(RB-P86)	-2104.112811

Structure:



Coordinates:

O	1.561893	-1.254890	-0.808468	H	2.889057	3.806954	-2.032334
C	-1.139776	-1.309683	0.304541	H	4.313709	4.149645	-1.017804
C	-1.707791	-1.712203	-0.910791	H	3.743954	2.469647	-1.211955
C	-1.010505	-2.166509	1.406783	H	1.475473	5.361165	1.147535
C	-2.094269	-3.047704	-1.044644	H	2.989371	5.806559	0.349320
H	-1.840213	-1.016356	-1.742045	H	1.552825	5.525715	-0.641843
C	-1.413886	-3.496849	1.253059	H	4.198048	3.931625	1.509919
H	-0.590891	-1.821482	2.353615	H	2.696165	3.410984	2.314912
C	-1.952864	-3.931438	0.035379	H	3.641010	2.243805	1.346715
H	-2.513937	-3.392786	-1.991759	C	-1.116426	1.258635	0.792800

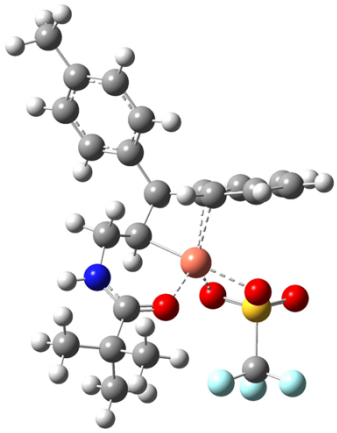
H	-1.309446	-4.188168	2.091630	H	-1.171146	2.069728	-1.241638
H	-2.278515	-4.968271	-0.070795	H	-1.965531	3.062526	-0.006032
Cu	0.267393	0.026231	0.072449	C	-2.282942	0.444707	1.050833
C	4.189283	-1.590710	-0.549683	H	-0.556085	1.466047	1.718554
F	5.131882	-2.313481	0.093411	C	-3.594005	0.469184	0.449880
F	4.271983	-1.854925	-1.871332	H	-2.277673	0.003473	2.049412
F	4.448895	-0.281712	-0.355554	C	-4.646388	-0.116307	1.202881
S	2.477434	-2.053901	0.112372	C	-3.917619	1.050134	-0.803531
O	2.393229	-3.499453	-0.112128	C	-5.955724	-0.093066	0.742557
O	2.445372	-1.557950	1.498413	H	-4.417875	-0.582791	2.164489
O	1.564183	1.500986	-0.087450	C	-5.228527	1.059084	-1.258245
C	1.341938	2.746042	-0.000496	H	-3.145232	1.478884	-1.441002
C	2.529706	3.704268	0.138937	C	-6.275693	0.496829	-0.496186
N	0.095497	3.236700	-0.023508	H	-6.747805	-0.542720	1.345808
C	3.420634	3.514388	-1.113848	H	-5.454901	1.506900	-2.228861
C	2.092930	5.177097	0.253325	C	-7.694267	0.547556	-0.988125
C	3.310859	3.288989	1.409739	H	-8.152724	1.515002	-0.718251
C	-1.096541	2.412051	-0.195710	H	-7.743603	0.462495	-2.083230
H	-0.028462	4.244884	0.040240	H	-8.308424	-0.244089	-0.537413

Cu(III)-OTf-arylatedallylicamideadduct-cation – towards enamide (Int-15):

Energies (Hartree):

Zero-point correction	0.435980
Thermal correction to Energy	0.470420
Thermal correction to Enthalpy	0.471365
Thermal correction to Gibbs Free Energy	0.365779
Sum of electronic and zero-point Energies	-2103.708675
Sum of electronic and thermal Energies	-2103.674234
Sum of electronic and thermal Enthalpies	-2103.673290
Sum of electronic and thermal Free Energies	-2103.778876
E(RB-P86)	-2104.144655

Structure:

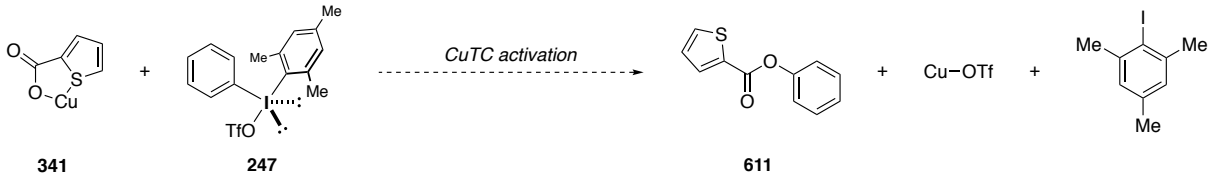


Coordinates:

O	-2.134859	-1.324615	0.856774	H	-1.507188	3.783813	2.723296
C	1.304370	-1.539932	0.348416	H	-2.961226	4.615544	2.117233
C	1.127608	-1.033112	1.675753	H	-2.845319	2.838509	2.011020
C	0.948340	-2.885357	0.079413	H	-0.454334	5.455086	-0.545255
C	0.622299	-1.865582	2.688347	H	-1.570987	6.089013	0.664012
H	1.482488	-0.034436	1.939894	H	-0.069616	5.325951	1.208229
C	0.460625	-3.696229	1.096309	H	-3.431456	4.758636	-0.390047
H	1.072463	-3.278907	-0.931240	H	-2.323911	4.004340	-1.564551
C	0.291254	-3.187372	2.398397	H	-3.334392	2.980876	-0.504406
H	0.502224	-1.471902	3.698745	C	1.062885	0.571745	-0.806606
H	0.201970	-4.734506	0.881537	H	2.078028	1.726716	0.721672
H	-0.100726	-3.834867	3.184957	H	2.298418	2.257241	-0.938226
Cu	-0.464170	-0.205874	0.251686	C	1.949051	-0.668143	-0.743981
C	-4.202057	-0.953092	-0.837295	H	0.437628	0.663971	-1.706826
F	-4.646155	-1.274880	-2.067532	C	3.444038	-0.405954	-0.611482
F	-5.099504	-1.368636	0.076354	H	1.788692	-1.203374	-1.693597
F	-4.081124	0.385337	-0.753802	C	4.129622	0.073473	-1.746366
S	-2.537827	-1.798219	-0.524090	C	4.176123	-0.635288	0.561147
O	-2.823643	-3.222685	-0.656435	C	5.499914	0.319696	-1.700400
O	-1.592067	-1.183327	-1.509408	H	3.583910	0.236768	-2.680496
O	-1.255791	1.563175	0.449370	C	5.554577	-0.394307	0.598485
C	-0.746590	2.712445	0.284686	H	3.686432	-1.021369	1.457674
C	-1.646363	3.935602	0.531193	C	6.241626	0.092725	-0.523937
N	0.517616	2.900680	-0.110089	H	6.009480	0.682823	-2.597211
C	-2.276223	3.774435	1.935656	H	6.105414	-0.591119	1.522023
C	-0.872844	5.265300	0.456504	C	7.725441	0.359775	-0.482673
C	-2.751411	3.909638	-0.554662	H	8.150288	0.117751	0.501225
C	1.540813	1.864409	-0.233223	H	8.255145	-0.238335	-1.241488
H	0.839040	3.865121	-0.180456	H	7.943706	1.417742	-0.700203

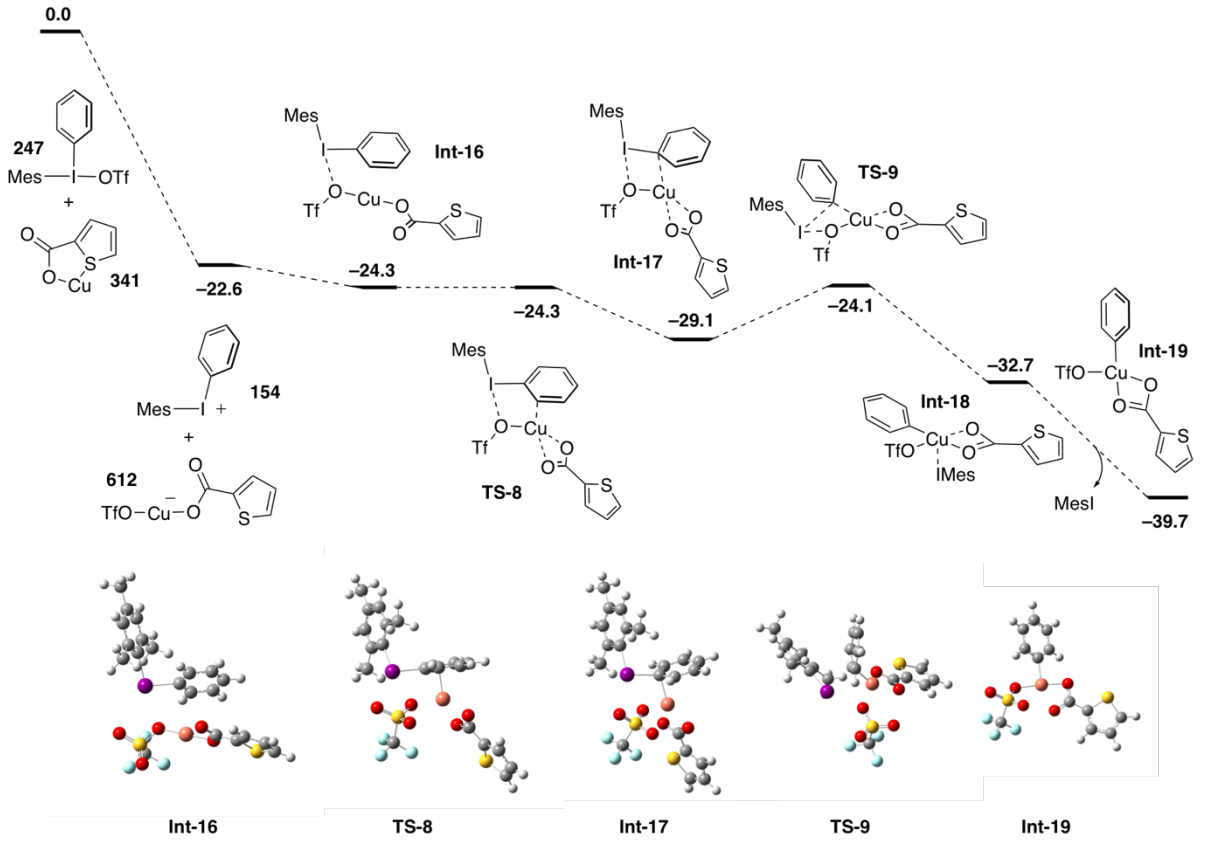
i.2.7 CuTC activation

It has been previously observed that reactions employing copper(I) thiophene-2-carboxylate (CuTC, **341**) give near catalyst-equimolar quantities of thiophene-coupled product **611**. It is thought that the active catalyst for these alkene functionalisation process is in fact copper(I) triflate rather than the more stable copper TC adduct. It is proposed that the following process to generate copper(I) triflate occurs in the early stages of these copper-catalysed reactions (Scheme 147).



Scheme 147 – Proposed generation of CuOTf from CuTC (**341**)

To assess the viability of this process, the following energy profile for the oxidative addition of CuTC (**341**) into phenyl(mesityl)iodonium triflate (**247**) was computed (Scheme 148).

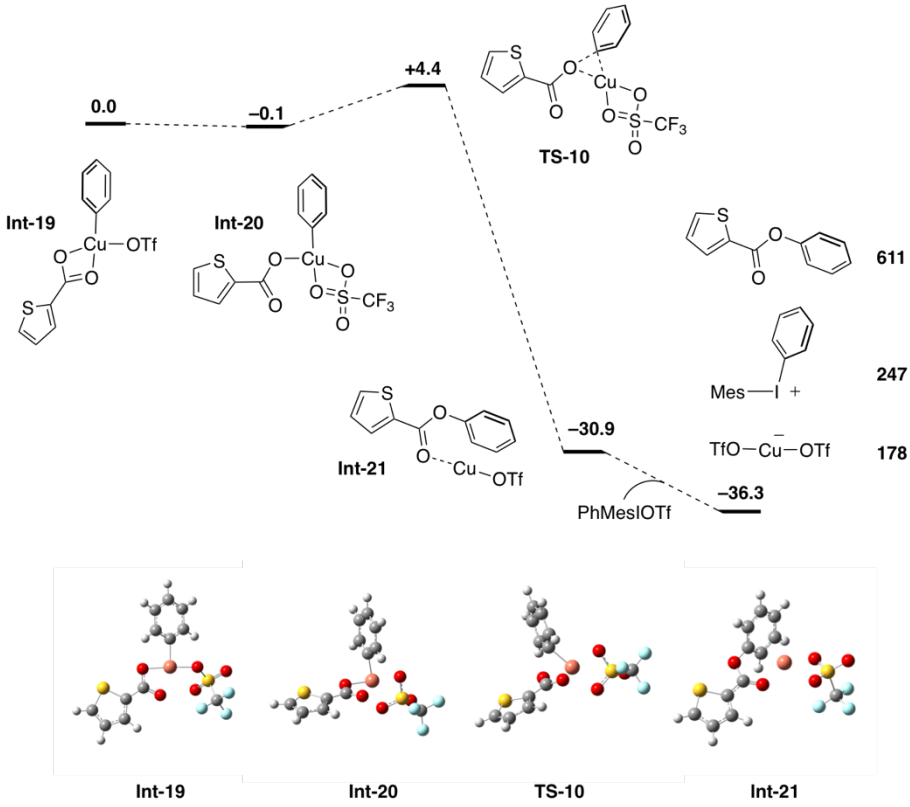


Scheme 148 – Oxidative addition of CuTC **341** with mesityl(phenyl)iodonium triflate **247** (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu,I], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

Formation of the pre-oxidative addition complex **Int-17** is observed to be thermodynamically downhill relative to all previous intermediate adducts. The energetic barrier to oxidative addition is computed to

be only 5 kcal mol^{-1}, proceeding through transition state **TS-9** to give the apical mesityl-iodide-bound aryl copper(III) species **Int-18**. Simple dissociation of the aryl iodide gives κ^2-TC bound Cu(III) intermediate **Int-19**.

Attention was next turned towards the reductive elimination process (Scheme 149). It is computed that κ^2-TC-bound species **Int-19** lies in equilibrium with the corresponding κ^2-triflate-bound adduct **Int-20**. Reductive elimination of this species is calculated to proceed with a barrier of 4.5 kcal mol^{-1} through transition structure **TS-10** to give the ester-bound copper(I) species **Int-21**. Dissociation of the coupled product and association of a triflate anion is computed to be thermodynamically favourable, giving copper(I) triflate anion **178** ready for a subsequent oxidative addition.



Scheme 149 – Reductive elimination of thiophene carboxylate-bound Cu(III) species **Int-19** to ultimately furnish copper(I) triflate anion **178** as the active catalyst for the alkene arylation procedure (Gaussian 09 - BP86 functional, Def2SVP (SDD) [Cu,I], 6-31G+(d,p) [C,H,O,F,S]); energies given as ΔG (kcal mol^{-1})

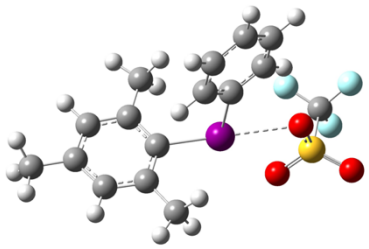
This overall process is computed to be highly exergonic, giving a net free energy change of −76.0 kcal mol^{-1} over the course of the reaction. This reaction scheme therefore represents a plausible mechanism by which these highly reactive copper(I) adducts may be generated *in situ* from bench-stable copper(I) sources. We anticipate that analogous mechanisms are followed to activate other commonly employed copper(I) salts such as copper(I) chloride and copper(I) iodide.

Phenyl(mesityl)iodonium triflate (247):

Energies (Hartree):

Zero-point correction	0.281520
Thermal correction to Energy	0.308191
Thermal correction to Enthalpy	0.309135
Thermal correction to Gibbs Free Energy	0.219043
Sum of electronic and zero-point Energies	-1553.724109
Sum of electronic and thermal Energies	-1553.697438
Sum of electronic and thermal Enthalpies	-1553.696494
Sum of electronic and thermal Free Energies	-1553.786587
E(RB-P86)	-1554.005629

Structure:



Coordinates:

C	-4.263199	-0.778468	0.869399	H	-1.603237	2.325780	0.382679
F	-5.060348	-1.872989	0.967602	C	1.918664	3.900346	-0.318770
F	-3.422446	-0.770437	1.938128	H	2.603769	1.860018	-0.651259
F	-5.048538	0.327075	0.942516	C	0.830867	4.726367	0.012301
S	-3.285286	-0.810003	-0.761016	H	-1.281537	4.800683	0.527684
O	-2.452592	-2.051939	-0.655651	H	2.903909	4.332201	-0.520965
O	-4.340587	-0.794503	-1.813046	H	0.966782	5.810707	0.069423
C	2.279651	-0.699211	0.021985	C	1.970273	-0.319253	2.556597
C	3.036763	-1.071397	-1.113743	H	1.618452	0.725137	2.484158
C	2.785001	-0.716827	1.346089	H	1.077795	-0.958161	2.675559
C	4.376262	-1.451248	-0.880493	H	2.574544	-0.407621	3.472354
C	4.129020	-1.106108	1.502728	C	2.495436	-1.081125	-2.527781
C	4.937742	-1.479511	0.409459	H	1.690109	-1.826252	-2.651054
H	4.991704	-1.737416	-1.741051	H	2.081111	-0.100534	-2.819629
H	4.552099	-1.119757	2.513996	H	3.295784	-1.333412	-3.240153
I	0.194886	-0.190264	-0.273101	C	6.372698	-1.905116	0.627212
C	0.485986	1.982468	-0.134888	H	6.419120	-2.853812	1.191541
C	-0.621796	2.768777	0.198877	H	6.900284	-2.052399	-0.328185
C	1.756172	2.503617	-0.398700	H	6.925380	-1.153008	1.216520

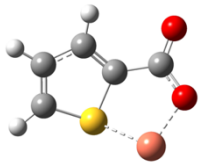
C	-0.430687	4.162837	0.268322	O	-2.463269	0.466707	-0.680901

Copper(I) thiophenecarboxylate (341):

Energies (Hartree):

Zero-point correction	0.067752
Thermal correction to Energy	0.076359
Thermal correction to Enthalpy	0.077304
Thermal correction to Gibbs Free Energy	0.032530
Sum of electronic and zero-point Energies	-936.632159
Sum of electronic and thermal Energies	-936.623552
Sum of electronic and thermal Enthalpies	-936.622607
Sum of electronic and thermal Free Energies	-936.667381
E(RB-P86)	-936.699911

Structure:



Coordinates:

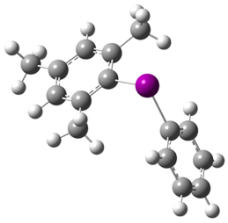
O	-1.795380	0.867956	0.108693	S	0.666036	-0.934099	0.620901
Cu	-1.426582	-1.014528	-0.268965	C	2.803399	0.083543	-0.429192
C	-0.676108	1.560432	0.148379	H	2.025292	2.155570	-0.777806
O	-0.620128	2.806883	0.190829	C	2.314458	-1.113306	0.051865
C	0.612278	0.768672	0.107264	H	3.826203	0.199877	-0.797576
C	1.838408	1.146622	-0.402441	H	2.832254	-2.063033	0.189519

Phenyl(mesityl)iodonium cation (154):

Energies (Hartree):

Zero-point correction	0.255672
Thermal correction to Energy	0.272667
Thermal correction to Enthalpy	0.273611
Thermal correction to Gibbs Free Energy	0.209533
Sum of electronic and zero-point Energies	-592.059802
Sum of electronic and thermal Energies	-592.042807
Sum of electronic and thermal Enthalpies	-592.041863
Sum of electronic and thermal Free Energies	-592.105941
E(RB-P86)	-592.315474

Structure:



Coordinates:

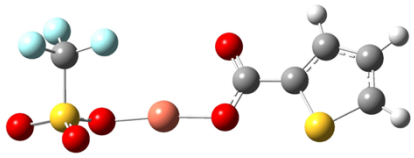
C	-1.241384	-0.232982	-0.192247	C	4.059153	1.806191	1.131753
C	-2.075324	-0.776277	0.810329	H	4.607346	2.092473	-0.954412
C	-1.533130	0.917268	-0.958832	H	3.295504	1.321933	3.111624
C	-3.282478	-0.083755	1.039669	H	4.833547	2.480426	1.509565
C	-2.757463	1.552444	-0.665331	C	-0.629331	1.478496	-2.031196
C	-3.642382	1.071513	0.319224	H	0.320149	1.851472	-1.608765
H	-3.960398	-0.474131	1.806953	H	-0.381112	0.719270	-2.793828
H	-3.019090	2.452369	-1.233231	H	-1.118987	2.321185	-2.541857
I	0.618893	-1.279744	-0.595083	C	-1.768794	-2.028000	1.602599
C	2.100725	0.104002	0.178949	H	-1.671632	-2.912567	0.949189
C	2.943696	0.726077	-0.752061	H	-0.833078	-1.932958	2.180183
C	2.199450	0.284257	1.564577	H	-2.581037	-2.231450	2.316414
C	3.936096	1.590024	-0.251437	C	-4.960946	1.763842	0.578013
H	2.841433	0.559657	-1.827320	H	-5.743141	1.366904	-0.095002
C	3.196473	1.158832	2.034198	H	-5.304455	1.603015	1.612382
H	1.537239	-0.230723	2.264123	H	-4.889811	2.847944	0.394148

Copper(I)(triflate)thiophenecarboxylate anion (612):

Energies (Hartree):

Zero-point correction	0.255672
Thermal correction to Energy	0.272667
Thermal correction to Enthalpy	0.273611
Thermal correction to Gibbs Free Energy	0.209533
Sum of electronic and zero-point Energies	-592.059802
Sum of electronic and thermal Energies	-592.042807
Sum of electronic and thermal Enthalpies	-592.041863
Sum of electronic and thermal Free Energies	-592.105941
E(RB-P86)	-592.315474

Structure:



Coordinates:

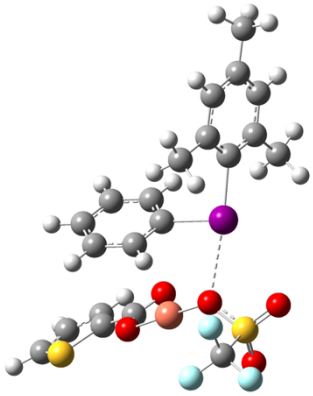
Cu	-0.300686	-0.709904	-0.556266	C	2.173705	0.369872	-0.463445
O	-2.150201	-0.860936	-1.017943	O	1.655815	1.378185	-1.004611
S	-3.260826	-0.748783	0.047354	C	3.623137	0.364332	-0.120910
C	-3.266183	1.116762	0.415023	C	4.557130	1.370620	-0.332119
O	-2.925063	-1.382440	1.352670	S	4.368620	-1.026257	0.647158
O	-4.597797	-1.024715	-0.541435	C	5.866489	1.026248	0.122030
F	-4.237650	1.415069	1.313939	H	4.288763	2.320448	-0.800737
F	-2.071972	1.502087	0.931335	C	5.919431	-0.243505	0.676088
F	-3.493992	1.829872	-0.714889	H	6.736299	1.683916	0.045238
O	1.539446	-0.735889	-0.148387	H	6.782773	-0.759386	1.099213

Copper(I)(triflate)thiophenecarboxylate – phenyl(mesityl)iodonium adduct (Int-16):

Energies (Hartree):

Zero-point correction	0.350511
Thermal correction to Energy	0.387893
Thermal correction to Enthalpy	0.388837
Thermal correction to Gibbs Free Energy	0.269901
Sum of electronic and zero-point Energies	-2490.411851
Sum of electronic and thermal Energies	-2490.374469
Sum of electronic and thermal Enthalpies	-2490.373525
Sum of electronic and thermal Free Energies	-2490.492461
E(RB-P86)	-2490.762362

Structure:



Coordinates:

C	-3.784968	-0.955902	-0.208250	H	-2.487037	-1.639336	-2.731817
C	-4.230739	-1.532936	-1.420709	H	-4.048551	-1.943148	-3.531028
C	-4.445351	-1.106602	1.033641	C	-7.364057	-3.345458	-0.104765
C	-5.397166	-2.322030	-1.343048	H	-8.244210	-2.710929	-0.317465
C	-5.602571	-1.911812	1.032997	H	-7.344874	-4.143551	-0.864595
C	-6.096657	-2.520692	-0.136816	H	-7.521775	-3.805228	0.884215
H	-5.767723	-2.789203	-2.262704	O	0.375316	1.797340	-0.262363
H	-6.131815	-2.058918	1.981483	Cu	1.983197	0.757701	-0.073414
I	-2.025470	0.314612	-0.289313	S	0.257859	3.217487	-0.890563
C	-0.671969	-0.968831	0.824965	C	0.423249	4.313744	0.655086
C	-0.081138	-0.439908	1.981526	O	-1.128582	3.443935	-1.377220
C	-0.439249	-2.268989	0.362734	O	1.402102	3.581972	-1.760160
C	0.782290	-1.276278	2.715156	F	0.261248	5.613049	0.314391
H	-0.282346	0.581256	2.314551	F	-0.520875	3.982592	1.568808
C	0.428264	-3.082551	1.115317	F	1.643132	4.158752	1.219198
H	-0.901520	-2.651912	-0.550068	O	3.587953	-0.215777	0.185955
C	1.033021	-2.589970	2.284921	C	3.763242	-1.120620	-0.749933
H	1.256187	-0.887141	3.621387	O	2.969034	-1.343295	-1.698581
H	0.631569	-4.101567	0.772289	C	5.017538	-1.910702	-0.619004
H	1.708274	-3.231406	2.859155	C	5.488319	-2.915442	-1.455234
C	-3.968256	-0.477004	2.322031	S	6.128485	-1.637185	0.711916
H	-2.980816	-0.868702	2.623423	C	6.735092	-3.464236	-1.027425
H	-3.873122	0.619383	2.229212	H	4.940058	-3.233467	-2.345063
H	-4.675763	-0.687720	3.138318	C	7.205084	-2.871648	0.134373
C	-3.548498	-1.339498	-2.758353	H	7.267401	-4.262208	-1.551532
H	-3.583321	-0.285619	-3.086459	H	8.124059	-3.091934	0.679753

TS to oxidative addition pre-complex (TS-8):

Energies (Hartree):

Zero-point correction	0.349647
Thermal correction to Energy	0.386084
Thermal correction to Enthalpy	0.387029
Thermal correction to Gibbs Free Energy	0.272842
Sum of electronic and zero-point Energies	-2490.415751
Sum of electronic and thermal Energies	-2490.379314
Sum of electronic and thermal Enthalpies	-2490.378370
Sum of electronic and thermal Free Energies	-2490.492557
E(RB-P86)	-2490.765399

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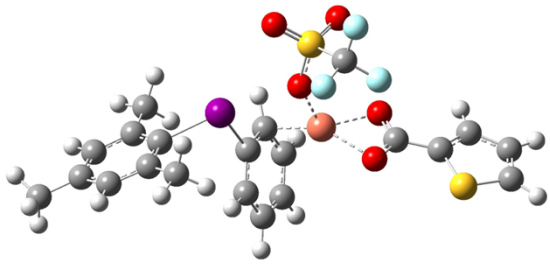


Coordinates:

C	-4.090410	-0.156269	0.212063	H	-4.892490	-1.378387	-2.939304
C	-4.766207	-0.762985	-0.874080	H	-3.829008	0.027665	-2.673845
C	-4.657133	0.022391	1.495445	C	-8.073806	-1.650055	0.881613
C	-6.067534	-1.237577	-0.617607	H	-8.536362	-1.202093	1.775424
C	-5.964912	-0.475301	1.677061	H	-8.731385	-1.463924	0.016110
C	-6.683304	-1.105215	0.643291	H	-8.041092	-2.744316	1.035370
H	-6.614960	-1.718395	-1.436590	O	0.550386	1.242423	-0.540454
H	-6.432602	-0.353928	2.660694	Cu	1.374355	-0.720985	-0.584807
I	-2.102204	0.649230	-0.132108	S	0.891021	2.682821	-0.967644
C	-1.050273	-1.243733	-0.283744	C	1.719752	3.367772	0.600781
C	-1.214990	-2.191981	0.734774	O	-0.341728	3.506772	-1.129247
C	-0.311107	-1.484280	-1.476690	O	1.934707	2.764642	-2.021494
C	-0.569957	-3.437247	0.591965	F	2.039372	4.673320	0.421491
H	-1.810418	-1.977015	1.625650	F	0.877691	3.274173	1.660952
C	0.392617	-2.726653	-1.541424	F	2.849875	2.682170	0.887658

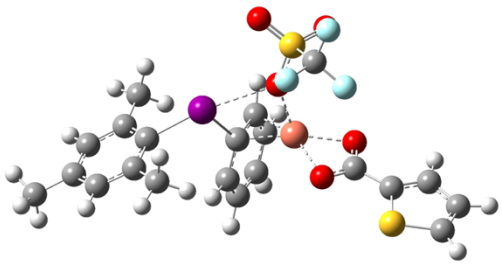
H	-0.406742	-0.843475	-2.359702	O	2.933472	-0.963784	0.786886
C	0.245931	-3.691669	-0.523354	C	3.787203	-1.097404	-0.175391
H	-0.689424	-4.191006	1.375729	O	3.424223	-1.036976	-1.402070
H	0.968049	-2.956802	-2.442834	C	5.209059	-1.330510	0.162342
H	0.772276	-4.646607	-0.609340	C	6.286336	-1.496423	-0.700184
C	-3.956531	0.712708	2.646780	S	5.725618	-1.426856	1.835773
H	-2.978711	0.253626	2.872950	C	7.522383	-1.701532	-0.017290
H	-3.776014	1.781086	2.433702	H	6.171536	-1.466424	-1.786089
H	-4.573302	0.655646	3.556708	C	7.374934	-1.689489	1.361417
C	-4.159383	-0.936063	-2.247728	H	8.483172	-1.851139	-0.516292
H	-3.280164	-1.603950	-2.220765	H	8.144961	-1.819146	2.123357

Oxidative addition pre-complex (Int-17):

Energies (Hartree):

Zero-point correction	0.349636
Thermal correction to Energy	0.386883
Thermal correction to Enthalpy	0.387827
Thermal correction to Gibbs Free Energy	0.270273
Sum of electronic and zero-point Energies	-2490.420800
Sum of electronic and thermal Energies	-2490.383553
Sum of electronic and thermal Enthalpies	-2490.382609
Sum of electronic and thermal Free Energies	-2490.500162
E(RB-P86)	-2490.770436

Structure:



Coordinates:

C	-3.742047	-0.080555	0.552517	H	-5.326509	0.097275	-2.533746
C	-4.691618	-0.198972	-0.492088	H	-4.122911	1.289719	-1.976227
C	-3.991695	-0.473537	1.890545	C	-7.574141	-1.824940	1.472831

C	-5.934176	-0.770601	-0.154209	H	-7.853025	-1.672366	2.527946
C	-5.257983	-1.034800	2.154967	H	-8.374806	-1.416266	0.834973
C	-6.237832	-1.192206	1.155505	H	-7.538341	-2.915834	1.295484
H	-6.687871	-0.879040	-0.942668	O	0.696045	1.530300	-0.558164
H	-5.481748	-1.349342	3.180869	Cu	1.064876	-0.592866	-0.882339
I	-1.844678	0.857208	0.115591	S	1.246322	2.946801	-0.792196
C	-0.935603	-0.888208	-0.980306	C	2.285093	3.219850	0.776724
C	-1.275234	-2.173038	-0.478289	O	0.181151	3.986620	-0.718578
C	-0.521710	-0.692748	-2.337784	O	2.220377	3.023649	-1.913350
C	-1.139964	-3.276649	-1.328622	F	2.841054	4.457046	0.755080
H	-1.618426	-2.303137	0.551387	F	1.506521	3.119716	1.883936
C	-0.403905	-1.844863	-3.165837	F	3.277822	2.304303	0.866392
H	-0.447536	0.307544	-2.775087	O	2.249238	-1.281420	0.768316
C	-0.711049	-3.114356	-2.667218	C	3.218249	-1.386886	-0.073738
H	-1.366515	-4.274502	-0.940647	O	3.039204	-1.081640	-1.315471
H	-0.099077	-1.711706	-4.208323	C	4.540778	-1.859642	0.375058
H	-0.629476	-3.989045	-3.319086	C	5.699032	-2.023554	-0.376814
C	-2.998947	-0.311783	3.022319	S	4.809964	-2.299375	2.050993
H	-2.029735	-0.789826	2.798779	C	6.798815	-2.503195	0.393976
H	-2.794959	0.752042	3.237561	H	5.737442	-1.799070	-1.445081
H	-3.394360	-0.767772	3.942787	C	6.466880	-2.699617	1.726120
C	-4.424384	0.229266	-1.917056	H	7.795614	-2.695810	-0.010345
H	-3.616138	-0.368051	-2.375141	H	7.106271	-3.056008	2.535006

Oxidative addition TS (TS-9):

Energies (Hartree):

Zero-point correction	0.349183
Thermal correction to Energy	0.385781
Thermal correction to Enthalpy	0.386725
Thermal correction to Gibbs Free Energy	0.271258
Sum of electronic and zero-point Energies	-2490.414309
Sum of electronic and thermal Energies	-2490.377711
Sum of electronic and thermal Enthalpies	-2490.376767
Sum of electronic and thermal Free Energies	-2490.492233
E(RB-P86)	-2490.763492

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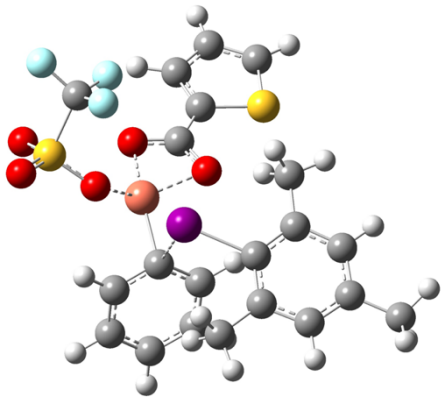


Coordinates:

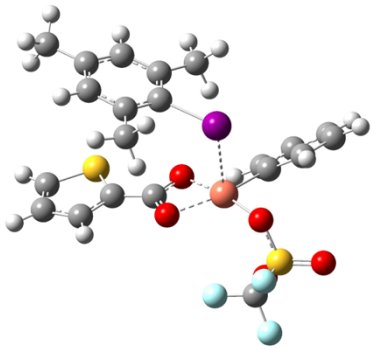
C	-3.146877	0.018757	-0.860343	H	-5.593790	-1.827291	0.776946
C	-4.380835	-0.410791	-0.309339	H	-4.309691	-2.581707	-0.205270
C	-2.987530	1.232436	-1.576090	C	-6.591216	2.570440	-1.328516
C	-5.485085	0.444170	-0.488617	H	-6.707524	3.208764	-0.432992
C	-4.136571	2.038104	-1.713972	H	-6.493164	3.238711	-2.199136
C	-5.387333	1.666990	-1.183982	H	-7.521343	1.988174	-1.435634
H	-6.452523	0.136893	-0.074793	O	1.224010	-2.016757	0.333739
H	-4.044779	2.981842	-2.263884	Cu	1.007731	-0.071524	0.992744
I	-1.437417	-1.253914	-0.647115	S	2.413942	-2.967108	0.082881
C	-0.786331	-0.410903	1.739633	C	2.849916	-2.578616	-1.728418
C	-1.460173	0.787640	2.037252	O	1.978618	-4.389325	0.056953
C	-0.634722	-1.459764	2.668490	O	3.630282	-2.615458	0.860752
C	-1.870377	0.992648	3.367301	F	3.899519	-3.339206	-2.124604
H	-1.614091	1.561993	1.280942	F	1.793969	-2.849940	-2.536872
C	-1.050801	-1.221569	3.993947	F	3.180350	-1.274507	-1.881910
H	-0.181164	-2.411202	2.380261	O	0.940722	1.946214	0.329043
C	-1.670554	-0.007506	4.338103	C	2.227596	1.968306	0.457950
H	-2.351517	1.939335	3.633869	O	2.834619	0.907199	0.867342
H	-0.905350	-2.006173	4.743585	C	2.987577	3.186146	0.150374
H	-2.013260	0.156229	5.364510	C	4.365667	3.370021	0.206853
C	-1.678370	1.681744	-2.184611	S	2.174356	4.649754	-0.370666
H	-0.874413	1.751467	-1.430047	C	4.763808	4.685843	-0.167727
H	-1.333355	0.977267	-2.962473	H	5.048865	2.572605	0.507273
H	-1.794595	2.671605	-2.652488	C	3.685275	5.490234	-0.505427
C	-4.553427	-1.715317	0.434723	H	5.799857	5.032011	-0.189878
H	-3.896498	-1.770112	1.320377	H	3.696117	6.532683	-0.826742

Copper(III)-K²-TC-OTf-Ph-apicalMesI (Int-18):

Energies (Hartree):

Zero-point correction	0.349719
Thermal correction to Energy	0.386947
Thermal correction to Enthalpy	0.387891
Thermal correction to Gibbs Free Energy	0.269128
Sum of electronic and zero-point Energies	-2490.425265
Sum of electronic and thermal Energies	-2490.388038
Sum of electronic and thermal Enthalpies	-2490.387093
Sum of electronic and thermal Free Energies	-2490.505856
E(RB-P86)	-2490.774984

Structure:



Coordinates:

C	-2.429221	-1.109712	-1.355033	H	-2.996295	-3.320822	1.259921
C	-3.047331	-1.850099	-0.322188	H	-1.948311	-3.715055	-0.133390
C	-3.106473	-0.140341	-2.128385	C	-6.592722	-0.347514	-0.495174
C	-4.409980	-1.580301	-0.072023	H	-7.131923	0.025410	-1.381533
C	-4.468056	0.078326	-1.825955	H	-7.107635	-1.251819	-0.130398
C	-5.138086	-0.627212	-0.808979	H	-6.684387	0.421989	0.293626
H	-4.911505	-2.144573	0.723545	O	2.619951	0.020180	-0.545735
H	-5.016421	0.822000	-2.416620	Cu	1.049325	0.022811	0.572781
I	-0.363566	-1.539839	-1.830263	S	3.931068	0.728688	-0.058419
C	1.660028	-1.569766	1.550458	C	4.032766	2.151622	-1.319140
C	1.357812	-1.568494	2.908619	O	5.126319	-0.104220	-0.327344
C	2.342515	-2.584000	0.884182	O	3.765498	1.371509	1.269865
C	1.774542	-2.694772	3.657033	F	5.164295	2.860112	-1.096848
H	0.810547	-0.754336	3.391210	F	4.063764	1.663413	-2.579416
C	2.734826	-3.700978	1.656999	F	2.969839	2.974476	-1.192270
H	2.587919	-2.532477	-0.178526	O	-0.493745	0.363140	1.705250
C	2.454600	-3.751872	3.032207	C	-0.785753	1.456071	1.033354
H	1.549488	-2.724604	4.728523	O	-0.006558	1.743399	0.054230

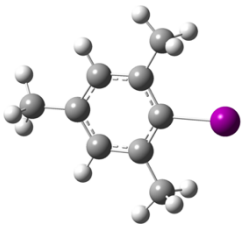
H	3.271531	-4.517338	1.161875	C	-1.927823	2.271289	1.406281
H	2.772130	-4.618678	3.620793	C	-2.322479	3.473606	0.820565
C	-2.455081	0.627964	-3.255368	S	-2.989092	1.822826	2.728156
H	-1.575794	1.195181	-2.902935	C	-3.477954	4.026528	1.436209
H	-2.100953	-0.050891	-4.051720	H	-1.785733	3.922538	-0.017898
H	-3.167609	1.338835	-3.702576	C	-3.947837	3.242697	2.481709
C	-2.324671	-2.891654	0.499905	H	-3.950743	4.961930	1.129103
H	-1.450353	-2.457222	1.016303	H	-4.811540	3.423277	3.123220

Mesityl iodide:

Energies (Hartree):

Zero-point correction	0.167168
Thermal correction to Energy	0.178604
Thermal correction to Enthalpy	0.179548
Thermal correction to Gibbs Free Energy	0.127293
Sum of electronic and zero-point Energies	-360.736878
Sum of electronic and thermal Energies	-360.725442
Sum of electronic and thermal Enthalpies	-360.724497
Sum of electronic and thermal Free Energies	-360.776753
E(RB-P86)	-360.904046

Structure:



Coordinates:

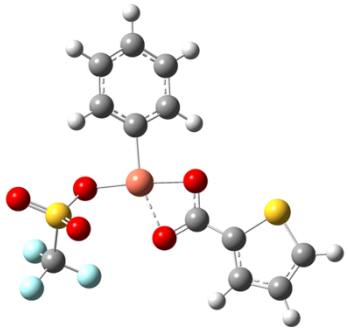
C	-0.180789	-0.000004	-0.000446	H	0.508950	-2.685094	0.881077
C	-0.854250	1.242204	-0.004738	H	-0.862885	-3.403716	-0.010961
C	-0.854239	-1.242209	-0.005055	C	-0.138587	2.573803	-0.006394
C	-2.266082	1.206496	-0.009983	H	0.508979	2.684847	0.881727
C	-2.266078	-1.206507	-0.010292	H	0.513658	2.680820	-0.891583
C	-2.990490	-0.000010	-0.009497	H	-0.862899	3.403712	-0.010052
H	-2.808546	2.159792	-0.016529	C	-4.505130	0.000001	0.018618
H	-2.808537	-2.159804	-0.017083	H	-4.880788	0.000769	1.058765
I	1.984515	0.000003	0.003431	H	-4.917808	0.893517	-0.478646
C	-0.138574	-2.573807	-0.007044	H	-4.917794	-0.894234	-0.477355
H	0.513713	-2.680580	-0.892232				

Copper(III)-K²-TC-OTf-Ph (Int-19):

Energies (Hartree):

Zero-point correction	0.182282
Thermal correction to Energy	0.205669
Thermal correction to Enthalpy	0.206613
Thermal correction to Gibbs Free Energy	0.124002
Sum of electronic and zero-point Energies	-2129.681909
Sum of electronic and thermal Energies	-2129.658522
Sum of electronic and thermal Enthalpies	-2129.657578
Sum of electronic and thermal Free Energies	-2129.740189
E(RB-P86)	-2129.864191

Structure:



Coordinates:

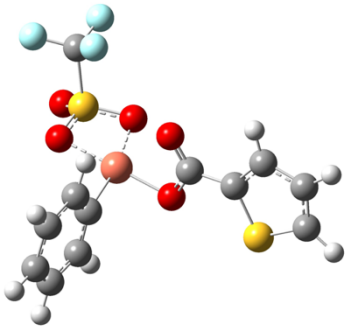
C	-0.649244	2.446595	-0.099710	O	-1.668428	-1.479879	1.730300
C	0.235990	3.283311	-0.771704	F	-3.155800	-3.625151	0.088809
C	-1.803653	2.857448	0.559425	F	-3.525798	-2.244444	-1.584592
C	-0.083686	4.661786	-0.788896	F	-1.467551	-2.817338	-1.066765
H	1.148386	2.919754	-1.251834	O	1.733583	0.894299	-0.016377
C	-2.083694	4.243894	0.538668	C	2.016064	-0.394749	-0.024160
H	-2.482646	2.162901	1.056431	O	1.011150	-1.188672	-0.090878
C	-1.232019	5.134524	-0.134125	C	3.392896	-0.842485	0.042752
H	0.589931	5.349053	-1.311857	C	3.846698	-2.161543	0.017576
H	-2.983565	4.602793	1.049557	S	4.723800	0.292838	0.171812
H	-1.464572	6.204231	-0.148176	C	5.262080	-2.251032	0.102156
O	-1.996302	0.048546	-0.275343	H	3.169759	-3.015181	-0.057861
Cu	-0.154584	0.539149	-0.092700	C	5.868144	-1.004482	0.189770
S	-2.596760	-1.071827	0.648109	H	5.820288	-3.189657	0.100290
C	-2.688284	-2.537443	-0.565057	H	6.932541	-0.777639	0.265741
O	-4.008158	-0.756830	0.968556				

Copper(III)-K²-OTf-TC-Ph (Int-20):

Energies (Hartree):

Zero-point correction	0.181862
Thermal correction to Energy	0.205408
Thermal correction to Enthalpy	0.206353
Thermal correction to Gibbs Free Energy	0.123141
Sum of electronic and zero-point Energies	-2129.681581
Sum of electronic and thermal Energies	-2129.658034
Sum of electronic and thermal Enthalpies	-2129.657090
Sum of electronic and thermal Free Energies	-2129.740302
E(RB-P86)	-2129.863443

Structure:



Coordinates:

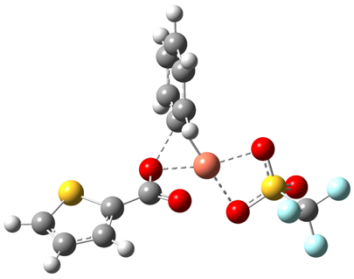
C	-0.274124	2.090353	0.036179	O	1.561089	-1.346859	-1.137414
C	-0.349705	2.371645	1.394795	F	3.952698	-2.672701	0.399725
C	-0.498229	2.986668	-1.002279	F	4.658952	-0.719836	1.131093
C	-0.618488	3.718794	1.735045	F	2.670587	-1.459502	1.711807
H	-0.202735	1.614273	2.168665	O	-1.405206	-0.103396	-0.793332
C	-0.763469	4.323559	-0.624286	C	-1.786599	-0.754327	0.308818
H	-0.471664	2.700577	-2.057253	O	-1.024234	-0.921087	1.285805
C	-0.822417	4.681443	0.732972	C	-3.166450	-1.264680	0.263212
H	-0.666800	3.990983	2.794690	C	-3.779592	-2.091658	1.200500
H	-0.929340	5.068064	-1.409948	S	-4.255361	-0.888270	-1.059607
H	-1.042628	5.716728	1.011878	C	-5.123656	-2.410693	0.857012
O	2.344012	0.800376	-0.313217	H	-3.263000	-2.441835	2.096800
Cu	0.398229	0.346230	-0.473865	C	-5.518629	-1.830400	-0.340489
S	2.838356	-0.579661	-0.822581	H	-5.780097	-3.038788	1.463688
C	3.580871	-1.417367	0.720817	H	-6.487487	-1.902841	-0.836687
O	3.918088	-0.555608	-1.823360				

Copper(III)-K²-TC-OTf-Ph – TS – Reductive elimination (TS-10):

Energies (Hartree):

Zero-point correction	0.181334
Thermal correction to Energy	0.204314
Thermal correction to Enthalpy	0.205258
Thermal correction to Gibbs Free Energy	0.123886
Sum of electronic and zero-point Energies	-2129.675712
Sum of electronic and thermal Energies	-2129.652733
Sum of electronic and thermal Enthalpies	-2129.651788
Sum of electronic and thermal Free Energies	-2129.733160
E(RB-P86)	-2129.857046

Structure:



Coordinates:

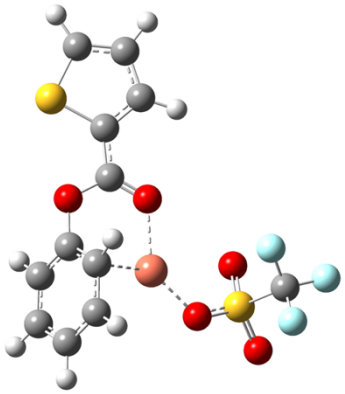
C	-0.729412	1.828283	0.037197	O	1.765907	-1.218089	-1.164370
C	-0.865743	2.074409	1.404586	F	4.227588	-2.474177	0.279420
C	-0.824815	2.787107	-0.973207	F	4.820510	-0.533933	1.132855
C	-0.991782	3.428016	1.782527	F	2.879060	-1.421927	1.662892
H	-0.843292	1.273493	2.147352	O	-1.523243	0.148005	-0.692186
C	-0.944679	4.127983	-0.556767	C	-1.798828	-0.768548	0.264174
H	-0.800373	2.520139	-2.033028	O	-0.939636	-1.094296	1.109366
C	-1.028319	4.444782	0.811681	C	-3.147927	-1.326140	0.195174
H	-1.060738	3.670732	2.847854	C	-3.652035	-2.376091	0.962206
H	-0.988124	4.915516	-1.315789	S	-4.351859	-0.723875	-0.930051
H	-1.143826	5.487625	1.121980	C	-5.003864	-2.682665	0.648781
O	2.421848	0.928696	-0.205096	H	-3.052290	-2.888828	1.717294
Cu	0.438065	0.312416	-0.412272	C	-5.513745	-1.870391	-0.356345
S	2.980009	-0.369535	-0.806251	H	-5.586131	-3.466367	1.138456
C	3.780179	-1.261199	0.670618	H	-6.515519	-1.884119	-0.788128
O	4.052301	-0.233899	-1.812654				

Copper(I)-OTf-phenolic ester adduct (Int-21):

Energies (Hartree):

Zero-point correction	0.183848
Thermal correction to Energy	0.207112
Thermal correction to Enthalpy	0.208056
Thermal correction to Gibbs Free Energy	0.123641
Sum of electronic and zero-point Energies	-2129.729106
Sum of electronic and thermal Energies	-2129.705842
Sum of electronic and thermal Enthalpies	-2129.704898
Sum of electronic and thermal Free Energies	-2129.789313
E(RB-P86)	-2129.912955

Structure:



Coordinates:

C	1.579809	2.058293	0.103819	O	-2.430022	0.626760	-0.344620
C	1.523182	3.003651	-0.927794	F	-4.385440	-0.844353	1.414041
C	0.712944	2.112715	1.231286	F	-4.197001	-2.740273	0.313383
C	0.571071	4.040131	-0.847243	F	-2.454022	-1.894364	1.356950
H	2.213693	2.924038	-1.771693	O	2.581530	1.074001	0.043573
C	-0.282688	3.130258	1.250555	C	2.185871	-0.247234	0.058262
H	0.919956	1.509576	2.123210	O	0.991233	-0.596885	0.108756
C	-0.340489	4.091931	0.220508	C	3.299624	-1.169930	0.000981
H	0.533171	4.794119	-1.638941	C	3.202170	-2.563198	-0.004270
H	-0.951025	3.202272	2.113622	S	4.973140	-0.643163	-0.073460
H	-1.096128	4.881591	0.259547	C	4.469919	-3.196770	-0.067207
O	-2.138858	-1.529864	-1.656460	H	2.242950	-3.083490	0.035514
Cu	-0.556675	0.822655	0.202056	C	5.516931	-2.283736	-0.108838
S	-3.086605	-0.632219	-0.940305	H	4.617463	-4.278549	-0.081411
C	-3.561878	-1.586549	0.633372	H	6.586947	-2.490918	-0.157882
O	-4.383711	-0.316009	-1.593914				

Copper(I)-OTf$_2$ anion (178):

See section 1.2.2

Thiophenyl phenolic ester (611):

Energies (Hartree):

Zero-point correction	0.156431
Thermal correction to Energy	0.168422
Thermal correction to Enthalpy	0.169366
Thermal correction to Gibbs Free Energy	0.115114
Sum of electronic and zero-point Energies	-972.531515
Sum of electronic and thermal Energies	-972.519524
Sum of electronic and thermal Enthalpies	-972.518579
Sum of electronic and thermal Free Energies	-972.572832
E(RB-P86)	-972.687946

Structure:

Coordinates:

C	-3.781988	0.606114	1.048653	O	-0.343894	-0.399852	0.077219
C	-2.378927	0.526030	1.051978	C	0.453896	0.685493	-0.249203
C	-1.745149	-0.228980	0.054866	O	0.013239	1.775953	-0.603380
C	-2.470927	-0.908185	-0.932361	C	1.875578	0.349099	-0.124036
C	-3.874532	-0.822708	-0.921474	C	2.940663	1.201719	-0.402342
C	-4.531015	-0.065882	0.065322	S	2.445785	-1.223679	0.408949
H	-4.288906	1.193712	1.820691	C	4.207557	0.591190	-0.187455
H	-1.784682	1.037153	1.814438	H	2.792339	2.226839	-0.748495
H	-1.940684	-1.492112	-1.690288	C	4.096151	-0.719680	0.252700
H	-4.452484	-1.349926	-1.687130	H	5.165593	1.090374	-0.347908
H	-5.623610	-0.001840	0.070228	H	4.897253	-1.419405	0.494677

xi Appendix 5 – Published Work

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Communication

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Enantioselective and Regiodivergent Copper-Catalyzed Electrophilic Arylation of Allylic Amides with Diaryliodonium Salts

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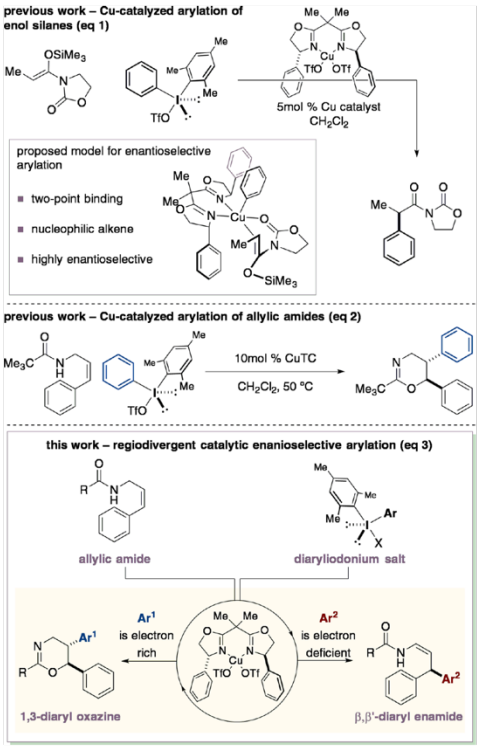
Supporting Information

ABSTRACT: A catalytic enantioselective and regiodivergent arylation of alkenes is described. Chiral copper(II)-bisoxazoline complexes catalyze the addition of diaryliodonium salts to allylic amides in excellent ee. Moreover, the arylation can be controlled by the electronic nature of the diaryliodonium salt enabling the preparation of nonracemic diaryloxazines or β,β'-diaryl enamides.

The catalytic asymmetric addition of carbon electrophiles to alkenes represents a strategically important bond-forming process. Successful examples of this have arisen from variations of the venerable Heck reaction,[1] with Sigman's enantioselective palladium-catalyzed addition of aryl diazonium salts and arylboronic acids to alkenols most notable.[2] Despite this remarkable transformation, catalytic enantioselective variants remain underdeveloped[3] and are in contrast to the burgeoning area of catalytic enantioselective halogenation.[4] Therefore, the identification of distinct strategies for the catalytic enantioselective addition of carbon electrophiles to unactivated alkenes remains an important challenge.

Over the last 7 years our laboratory has explored the novel reactivity of a putative copper(III)-aryl species as an aromatic electrophile equivalent.[5−7] These high oxidation state organometallics can be catalytically generated by the combination of simple copper complexes and diaryliodonium salts, and we have shown that a range of latent nucleophiles undergo site-selective arylation reactions to form synthetically versatile products. An important facet of many of these reactions is the presence of a proximal carbonyl group that steers reaction of the substrate. In addition to these studies, our group,[6d] as well as that of MacMillan,[7b,c] has also shown that copper−bisoxazoline complexes can function as excellent catalysts for enantioselective arylation reactions between electron-rich alkenes and diaryliodonium salts (eq 1). A proposed pathway for these reactions involves the electrophilic Cu(III)-aryl center engaging the carbon−carbon double bond through a two-point binding mode with a proximal carbonyl group, organizing the substrate for selective insertion to the Cu(III)−aryl bond. In light of these advances, we questioned whether these enantioselective arylation tactics could be merged with a carbonyl-directed oxy-arylation of alkenes (eq 2).[6f]

Here we report the successful realization of this idea through a copper-catalyzed enantioselective arylation of allylic amides with diaryliodonium salts (eq 3). Chiral copper(II)bisoxazoline catalysts impart high enantioselectivity in an oxy-arylation process wherein arylation takes place at alkene position proximal to the carbonyl, to form 1,3-oxazines. During our studies, we also discovered a remarkable electronic effect that enabled enantioselective arylation at the other position on the double bond leading to a β,β'-diaryl enamide. Together, this represents an electronically controllable regiodivergent enantioselective alkene arylation which forms synthetically versatile nonracemic products from a single starting material.[8,9]



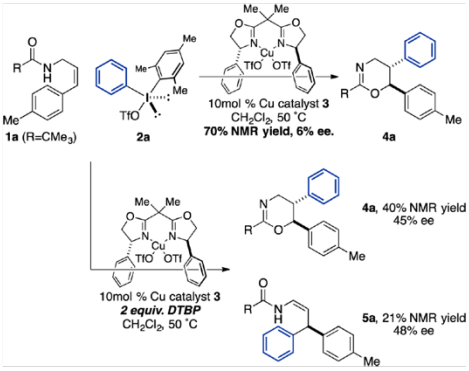
At the outset of our studies, we focused on creating a catalytic enantioselective variant of an endo selective oxy-arylation of allylic amides, that we had recently published using CuTC as the

Received: April 16, 2015
Published: June 19, 2015

DOI: 10.1021/jacs.5b03937
J. Am. Chem. Soc. 2015, 137, 7986−7989

catalyst (eq 2).[6f] Treatment of alkene **1a** with the diaryliodonium salt **2a** in the presence of copper(II) bisoxazoline catalyst **3** at room temperature,[6d] conditions similar to our enantioselective arylation of enol silanes, disappointingly returned only starting material. Pleasingly, reaction at 50 °C afforded a 70% yield (by ^{1}H NMR) of the desired 1,3-oxazine product **4a** but with only a 6% enantiomeric excess (Scheme 1). The reaction of diaryliodonium triflates in such a reaction is accompanied by the formation of trifluoromethanesulfonic acid, which we speculated might lead to decomposition of the chiral catalyst ultimately leading to a racemic reaction. To counter this, we added 2 equiv of the hindered base, 2,6-ditertbutylpyridine (DTBP), to the reaction. Although we were pleased to observe the formation of the oxazine **4a**, this time with 45% ee, we were surprised to find that the reaction also produced a second product determined to be *β*,*β*′-diarylenamide **5a** in 21% yield and 48% ee. While 1,3-oxazine **4a** is constructed via arylation at the alkene carbon atom proximal to the amide motif and is accompanied by concomitant carbon−oxygen bond formation, *β*,*β*′-diaryl enamide **5a** is the result of arylation at the other end of the double bond, accompanied by alkene transposition into conjugation with the amide group.

Scheme 1. Discovery of Regiodivergent Arylation



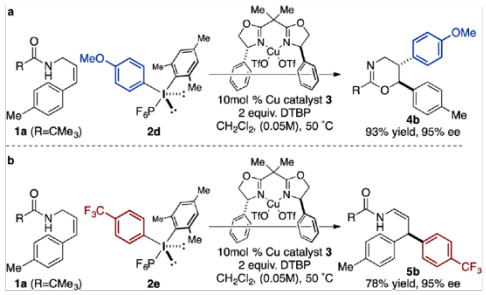
In order to further investigate this unusual regioselective arylation, we varied the counteranion of the diaryliodonium reagent and found changing from the OTf to the PF_6 salt[10] resulted in a small increase in the regioselectivity but huge improvement in enantioselectivity for both the oxazine (to 98%) and enamide (to 94%) products (Table 1, entries 1 and 2). A brief survey of solvents revealed consistently high ee for both products but a loss in regioselectivity and reactivity (entries 2−5), and so dichloromethane was retained as the optimum reaction medium. Use of the symmetrical diphenyliodonium hexafluorophosphate salt did not significantly change the regioselectivity, but the ee of the enamide was lower (entry 6). However, when we changed the electronic nature of the transferring aryl group from phenyl to 4-methoxyphenyl (**2d**), we were surprised to find that the 1,3-oxazine was formed exclusively in 93% assay yield and in 95% ee (Scheme 2a). This selectivity was further exemplified when we reversed the electron nature of the aryl group; the electron-deficient diaryliodonium salt **2e** gave exclusively the *β*,*β*′-diaryl enamide product in 78% assay yield and 95% ee (Scheme 2b).[11]

Table 1. Optimization of Regiodivergent Arylation

entry	[Ar−I−Ar′]X (**2**)	solvent	yield %[a] **4a**:**5a**	ee %[b] **4a**, **5a**
1	[Mes−I−Ph]**OTf**	CH_2Cl_2	40:21	45, 48
2	[Mes−I−Ph]$\mathbf{PF_6}$	CH_2Cl_2	65:26	98, 94
3	[Mes−I−Ph]$\mathbf{PF_6}$	1,4 dioxane	5:0	90, –
4	[Mes−I−Ph]$\mathbf{PF_6}$	1,2-DCE	34:25	95, 94
5	[Mes−I−Ph]$\mathbf{PF_6}$	PhMe	27:33	93, 93
6	[Ph−I−Ph]$\mathbf{PF_6}$	CH_2Cl_2	70:26	96, 88

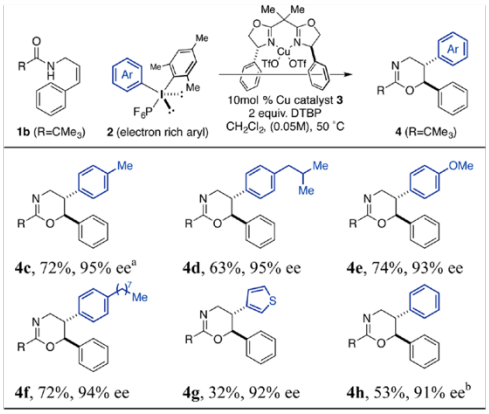
[a]Yield measured by 1H NMR against an internal standard. [b]Measured by chiral HPLC.

Scheme 2. Electronically Controlled Regiodivergent Arylation



Encouraged by these results, we next explored the regiodivergency of the arylation process using a single, electronically unbiased alkene. Focusing initially on the oxy-arylation of alkenes to form 1,3-oxazines, we found that a selection of electron-rich aryl groups could be transferred from the corresponding unsymmetrical aryl(mesityl)diaryliodonium hexafluorophosphate salts (Table 2a). In most cases the yields of the oxy-arylation process were good and accompanied by excellent enantioselectivities in the products (**4b**−**f**); only the

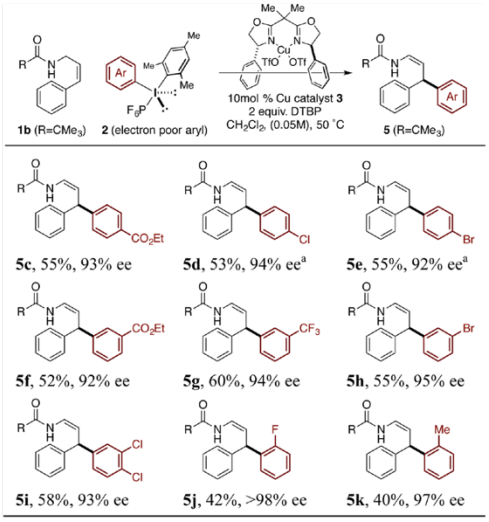
Table 2a. Enantioselective Aryl Transfer to Form Oxazines



[a]15 mol % **3** employed. [b]28% diphenyl enamide is isolated.

DOI: 10.1021/jacs.5b03937
J. Am. Chem. Soc. 2015, 137, 7986−7989

Table 2b. Enantioselective Aryl Transfer to β,β'-Diaryl Enamides



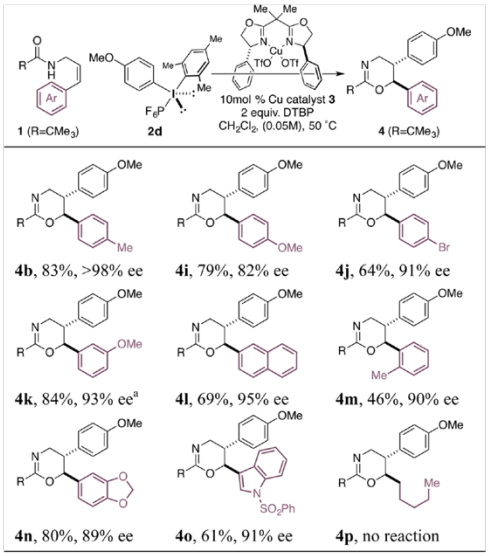
[a]4–8% (by NMR) of the corresponding oxazine product is observed.

oxazine product was observed. Although the transfer of a thiophene group proceeded in lower yield the ee was high (**4g**). Interestingly, the limit of the electronic control of the diaryliodonium salt extended to the transfer of a phenyl moiety; here, we observed the formation of the oxazine product in high ee and 53% yield (**4h**), but the reaction was accompanied by the formation of 32% of the corresponding achiral β,β'-diphenyl enamide (product not shown). Oxazine **4h** was crystalline, enabling identification of the absolute configuration by single crystal X-ray diffraction.[12]

When we examined the transfer of electron-deficient aryl groups to alkene **1b**, we found that the enamide was usually the exclusive product (Table 2b). Aryl groups displaying ester, halogens, and trifluoromethyl groups in the para and meta positions all worked well to produce the expected enamide products (**5b–i**). Small amounts of the corresponding oxazine (4–8%) were observed in the reactions transfering of *p*-Cl(C_6H_5) and *p*-Br(C_6H_5) groups. *o*-Fluoroaryl groups could also be accommodated and proceeded with moderate yield but excellent ee to form **5j**. Interestingly, transfer of the electron-donating *o*-tolyl group also formed the enamide product in high ee (**5k**). This result is in contrast to other electron-rich salts that generate the oxazine products and suggests there may be a subtle steric effect involved in determining the reaction selectivity.

We next investigated the scope of the alkene substrate in this process with a range of aryl-substituted allylic amides and either an electron-rich or electron-deficient aryl(mesityl)iodonium hexafluorophosphate. In general, substrates with electron-donating or neutral substituents on the aryl group of the alkene were highly reactive toward the 4-methoxyphenyl(mesityl)-iodonium salt (**2d**) and gave oxazine products in high yields and enantioselectivities (Table 3a). Synthetically versatile methoxy and halogen substituents can be positioned at various points on the aryl motif to afford oxazines in high yield and enantiomeric excess (**4a**, **4i–k**). 2-naphthyl, *o*-tolyl, and the pharmaceutically

Table 3a. Alkene Scope in the Enantioselective Oxy-Arylation

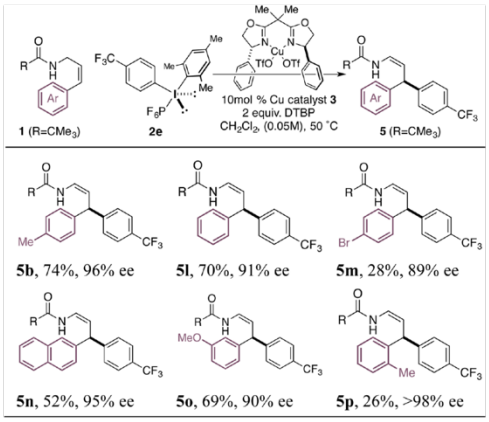


[a]15 mol % **3** employed.

common 1,3-benzodioxozole and 3-indole motifs also worked well to generate potentially interesting diarylated scaffolds in high ee (**4l–o**). Alkenes substituted with alkyl groups did not react in the oxy-arylation process (**4p**).

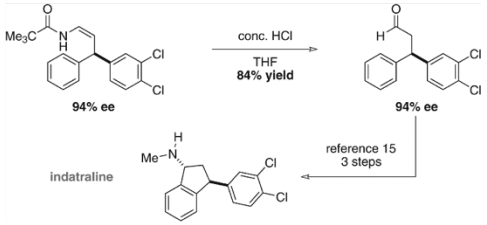
Using electron-deficient diaryliodonium salt **2e**, a similar set of allylic amides underwent arylation to β,β'-diaryl enamides (Table 3b). Here we observed that the allylic amide needed an electron-donating alkene substituent to impart sufficient reactivity. Despite this, a number of alkenes performed well in the reaction to form the β,β'-diaryl enamides with high enantioselectivity. β,β'-Diaryl enamide **5l** was crystalline, enabling identification of the absolute configuration by single crystal X-ray diffraction.[12]

Table 3b. Enantioselective Arylation to β,β'-Diarylaldehydes



DOI: 10.1021/jacs.5b03937
J. Am. Chem. Soc. 2015, 137, 7986–7989

Scheme 3. Application of β,β-diaryl enamides



Particularly appealing about the enantioselective arylation to form the β,β'diaryl enamides is their hydrolysis to the corresponding aldehyde; enantioenriched β,β'-diaryl aldehydes are useful building blocks that have a range of potential applications.[13] Acidic hydrolysis of enamide **5i** was performed in 84% yield. The resulting aldehyde **6** could be converted into indatraline **7**, a nonselective monoamine transporter inhibitor that has shown promise in the treatment of cocaine addition (Scheme 3).[14,15]

In summary, we have discovered an electronically controlled, regiodivergent copper-catalyzed enantioselective arylation of allylic amides. The electronic properties of the diaryliodonium salt can be used to affect the position of alkene arylation leading to either 1,3-oxazines or β,β'-diaryl enamides with high enantioselectivity. The process uses readily available starting materials, commercial catalyst and bisoxazoline ligand and is operationally simple. Although at present, the factors that control the regio- and enantioselectivity of the arylation process remain unclear, work is ongoing to elucidate the fascinating selectivity that control these transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03937.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to EPSRC, GSK, and the University of Cambridge (E.C., H.P.J.M., and M.T.) and the ERC and EPSRC for fellowships (M.J.G.). Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. We are grateful to Dr. Luke Humphries (GSK) for useful discussion.

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(11) Reaction using Cu(I)OTf·bisoxazoline catalysts gave comparable yield and ee (**5h**, 58% yield and 93% ee)
(12) Interestingly, the products **4h** and **5l** appear arise from arylation on different faces of the alkene using the same chiral catalyst. This suggests distinct regio- and enantiocontrol elements could be operating for each arylation pathway.
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J. Am. Chem. Soc. 2015, 137, 7986−7989